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## Original Communications

### THE DIAGNOSIS AND TREATMENT OF TRACHEAL AND ESOPHAGEAL OBSTRUCTION DUE TO CONGENITAL VASCULAR RING

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PRIOR to 1925, the congenital anomaly characterized by a double aortic arch was reported as a pathologic curiosity. In that year Arkin<sup>1</sup> wrote the first roentgenologic account of this condition. The patient was a 50-year-old man. The accuracy of this observation was verified at post-mortem examination.

Medical treatment of this condition has not been satisfactory. The symptoms are frequently distressing and progressive. Those patients fortunate enough to survive may be forced to subsist on soft solid and liquid diets. Others die of suffocation or repeated pulmonary infections. Some succumb as a result of a tracheotomy, which obviously cannot be expected to provide relief.

In 1933, Sprague and associates<sup>15</sup> stated their belief that surgical intervention "presents intriguing theoretical possibilities" and was justified in patients with this anomaly if dyspnea or dysphagia were predominant symptoms. The following quotation is from their paper:

So far as we know there has never been any surgical approach to the relief of pressure symptoms, but it presents intriguing theoretical possibilities. . . . Specifically, the hope in such cases would be to find an obliterated ductus arteriosus or remnant of the left fourth arch which could be divided or removed to allow more anterior and lateral mobility of the esophagus and trachea, even though the aortic arch continued to exert pressure from behind.

The following case reports represent two examples of surgical intervention for this condition.

#### CASE HISTORIES

CASE 1.—L. B., a 3½-month-old male, entered the Massachusetts General Hospital on May 17, 1945, because of paroxysmal cough and wheezy breathing first noticed ten days after birth.

From the Children's Medical and the Surgical Services of the Massachusetts General Hospital, Boston.

*Past History.*—The patient was born at term. Delivery was normal. The birth weight was 8 pounds, 7 ounces. The mother was not aware that the child had any unusual signs or symptoms while in the hospital, nor were any listed in the hospital record. The infant's diet was adequate, except that no vitamin D was given.

On the tenth day of the child's life he experienced a severe paroxysm of coughing, during which he became cyanotic. From that time on he had recurring attacks, sometimes four or five each day. They usually lasted only a few minutes and tended to subside abruptly. Those that occurred with feeding were accompanied occasionally with vomiting. The respirations were of a "wheezy" character, but they became normal while he was asleep. When the child was 1½ months old the family physician made a diagnosis of "croupy bronchitis."

By the time the baby was 2½ months old, the paroxysms of coughing and almost continuous wheezing had become more severe and he was admitted to a hospital. On admission, the temperature was found to be 101° F. rectally. A roentgenogram of the chest showed marked increased density of both hilar regions. A diagnosis of virus pneumonia was made. The child continued to have a low level of fever for the next twelve days. He breathed quietly while asleep but wheezed while he was awake, especially during feedings. Sulfadiazine was administered for seven days without benefit. In spite of his difficulties, however, he continued to gain weight.

On the twenty-ninth hospital day the baby became cyanotic while being fed and was transferred to the Massachusetts General Hospital.

*Physical Examination.*—On admission to this hospital the child was in no acute distress. He was a well developed, well nourished, 3½ month old infant. The anterior fontanel was open. His respirations were noisy, and if he became excited he developed inspiratory stridor. There were no signs of acute upper respiratory infection. The trachea was in the midline.

The chest was symmetrical and both sides expanded equally. There was no Harrison's groove. The chest circumference was 16 inches. There was slight inspiratory supraclavicular, sternal, and intercostal retraction. Percussion over the lung fields revealed no abnormality. The breath sounds were obscured by loud inspiratory and expiratory noises transmitted from the trachea. A direct laryngoscopy was performed by Dr. John Richardson and the larynx was found to be entirely normal.

His weight was 14 pounds 5 ounces, length, 26 inches. His temperature was 99.8° F., and his blood pressure was 100/50.

*Laboratory Data.*—The urine was negative. The red blood cell count was 3.56 million; hemoglobin, 9.75 Gm. per cent; white blood cell count, 12,750, with normal differential. Tuberculin test 1:1,000 was negative and the Hinton test was negative. The serum calcium was 11 mg. per cent; inorganic phosphorus, 6.5 mg. per cent; alkaline phosphatase, 11 Bodansky units; nonprotein nitrogen, 32 mg. per cent; and serum protein, 5.5 Gm. per cent.

Roentgenologic examinations of the esophagus with the aid of barium showed an indentation posteriorly at the level of the aortic arch (Fig. 1). Slightly caudal to this there was an indentation of the right lateral margin of the esophagus (Fig. 2). Taking the child's symptoms into consideration, these findings suggested a right sided aortic arch with a vascular ring about the esophagus and trachea. Nothing pathognomonic was noted in the neck, upper mediastinal shadow, or chest by plain chest films. Roentgenograms of the wrist showed no evidence of rickets.

*Course.*—The child's temperature remained normal. He wheezed continuously and had frequent episodes of coughing. He took most of his feedings well, but at one feeding he had considerable difficulty in swallowing, and became limp and cyanotic. However, he recovered in a few minutes.

*Diagnosis.*—Several causes of stridor in infants were considered at first. The observed concentrations of serum calcium, inorganic phosphorus, and phosphatase excluded a diagnosis of neonatal, rachitic, or hypoparathyroid tetany. Rickets was further excluded by the negative roentgenographic examination of the wrists.

The laryngoscopic examination readily excluded any abnormality of the larynx, and roentgenograms of the chest proved that the difficulty was not caused by absence of tracheal rings.

The diagnosis of right-sided aorta and congenital vascular ring constricting the esophagus was therefore established on the basis of roentgenologic examination of the esophagus with the aid of barium.

Dr. Paul D. White concurred in the opinion that an anomalous vascular ring was the probable cause of the respiratory and esophageal difficulties, and agreed that operative intervention was justified.



Fig. 1.

Fig. 1.—Case 1. Lateral view of esophagus following ingestion of barium. Arrow points to posterior indentation.

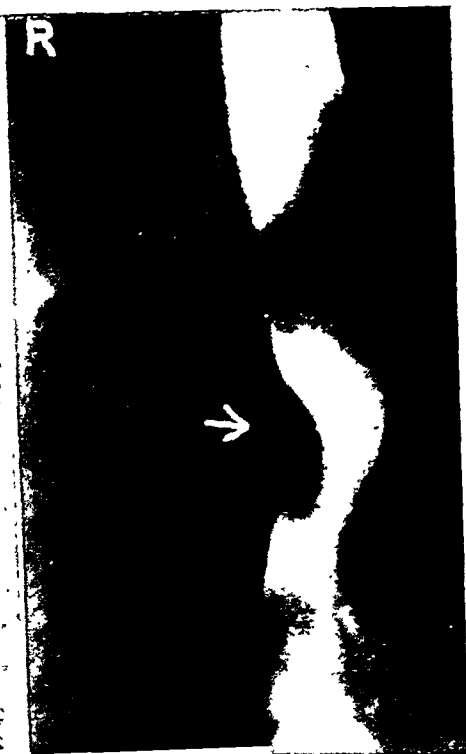


Fig. 2.

Fig. 2.—Case 1. Postero-anterior view of barium-filled esophagus. Arrow indicates the lateral impression caused by right aortic arch.

*Operative Findings and Procedure.*—On July 12, 1945, under ether-oxygen intratracheal anesthesia, an operation was performed. The incision was made through the fifth intercostal space on the left side. When the pleura and pericardium overlying the great vessels had been retracted, an unusual vascular arrangement was encountered (Fig. 3). There was a right or dorsal aortic arch which arose from the usual location at the base of the heart. This ascended and curved over the right main bronchus. It proceeded posteriorly and behind the esophagus, emerging from the left posterolateral aspect of that structure. Here it was joined by another, much smaller vessel, which arose from the first described vessel about one centimeter above its cardiac origin and passed in front of the trachea and esophagus. From this junction the artery descending in the normal course of the descending aorta along the left side of the vertebral column.

It was evident that these two vessels represented a doubled aortic arch of which the dorsal component carried the major blood load. The anatomy to the right of the trachea and esophagus could not be clearly visualized, but it appeared that the right common carotid and subclavian arteries arose separately from the larger vascular trunk on that side. The anterior vessel, or left aortic arch, sloped slightly to the left and posteriorly. At approximately its midportion there arose a long slender artery which extended through the superior mediastinum to the dome of the left chest where it branched into the common carotid, subclavian, and internal mammary arteries. This vessel was actually a left innominate artery. A patent ductus arteriosus connected the undersurface of the left arch with the pulmonary artery on that side at a point approximately one centimeter distal to the origin of the left innominate artery. The left recurrent laryngeal nerve passed beneath the anterior arch just lateral and posterior to the ductus. It then proceeded superiorly along its usual pathway.

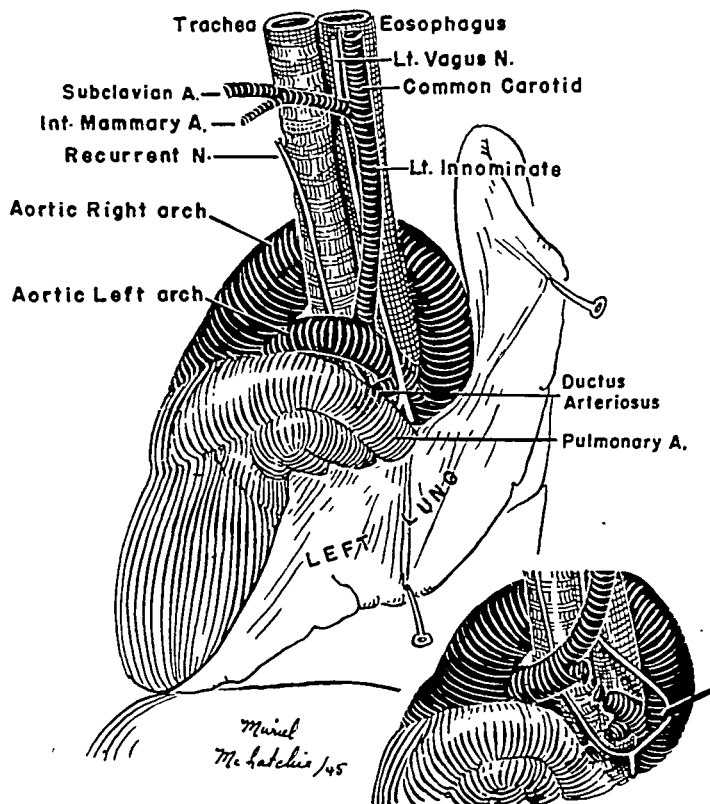


Fig. 3.—Case 1. Diagram illustrating left anterolateral view of the great vessels and their relations. Inset to demonstrate interruption of the vascular ring following ligation and division of the left arch and the patent ductus arteriosus.

After this anatomy was surveyed, the ductus arteriosus was occluded by external pressure, and no untoward effect was noted. It was then divided between two ligatures of braided silk. The ventral component of the double aortic arch was similarly compressed at a point between the innominate artery and the stump of the ductus. No appreciable change of vital signs was observed. The color of the upper extremities remained normal and the radial pulses did not change. Division of this vessel between ligatures was therefore performed at the site of compression. A sudden shift in the great vessels occurred immedi-

ately (Fig. 3 inset). The left innominate artery retracted superiorly and anteriorly. The exposed portion of the dorsal aortic arch receded slightly posteriorly and to the right. The trachea and esophagus appeared to bulge forward and to the left. They were now completely free from constriction. The operation was terminated in the usual manner. The patient withstood the procedure well and was returned to his crib in good condition. No change in the color or temperature of the extremities was ever noted.

*Postoperative Course.*—Postoperatively, the patient made an uneventful recovery. He received oxygen on his first postoperative day. After he had been on the ward for a few hours, he tolerated a 2 per cent whole milk and Karo formula. His airway was kept clear by frequent aspirations of mucus from his nasopharynx. The temperature rose to 101° F. on the first postoperative day, and returned to normal two days thereafter. It remained normal during the remainder of the child's stay in the hospital. The respiratory rate was 50 on the first postoperative day, but soon dropped to 30, and this rate was maintained until discharge. The character of his respirations was noticeably improved, except during excitement when there was a tendency to wheezing. While crying, he became slightly cyanotic, but he suffered no dysphagia and took his feedings without any of the alarming symptoms observed preoperatively. The respirations appeared to be entirely normal while he was sleeping and when he was undisturbed.



Fig. 4.—Case 1. Postoperative lipiodol bronchogram with coincidental filling of the esophagus. Arrows indicate right lateral impression of the esophagus and narrowed left main bronchus (see text). An arrow also points to the descending aorta on the left.

Postoperative roentgenograms of the chest showed both lung fields clear; the upper mediastinal shadow was not abnormal. A bronchogram was performed on July 23, 1945, under ether anesthesia (Fig. 4). The right, lateral margin of the trachea was slightly indented by the aortic arch on that side. Just distal to this impression the trachea deviated sharply to the right. The left main bronchus branched from the trachea at a more acute angle than normally. Narrowing of the midportion of this bronchus was noted. The main bronchus on the right was normal, as were all secondary bronchi. Some lipiodol spilled over into the esophagus and the indentation of its right lateral aspect, noted before operation, was still present. On physical examination, rhonchi could still be heard, apparently transmitted from the laryngeal region, but otherwise nothing unusual was found. He was discharged July 28, 1945, to be followed in the Outpatient Department.

The baby did well at home and gained weight steadily. He experienced no dysphagia. The cry, which had been somewhat weak, became stronger. The wheezing tendency diminished until he developed an upper respiratory infection, when the wheeze became more noticeable. In spite of this infection he continued to eat well and gained weight. Roentgenograms of the chest revealed normal heart and lungs.

*Embryologic Considerations*—The anomaly found in our first patient is quite unique when compared with anatomic descriptions of double aortae in the literature. Whereas the majority of reports state that the left subclavian and common carotid arteries arise separately from the ventral or left arch,<sup>16</sup> (Fig 5, B) these vessels in this instance branch from an innominate artery which in turn originates from the left arch. To explain the development of such an arrangement, it is necessary to present a different concept of embryologic development from that which has usually been proposed.

Congdon<sup>5</sup> has described fully the evolution of the aortic arch system in the human embryo. Only the essentials of this subject will be presented here.

In the second week of embryonic life, there exists a single chambered heart. On each side of this there is an ascending or ventral aorta, an aortic arch, and a dorsal aorta. Toward the end of the fourth week (5 mm embryo) the ascending segments unite to form the truncus arteriosus and the dorsal aortae combine to form a common descending aorta at a lower somatic level. Six aortic arches soon develop on each side. These connect the anterior and posterior trunks (Fig 5, A). They do not appear at the same time, and some of them regress completely. While they are present, the anlagen of the trachea and esophagus are encircled. Normally, the external carotid arteries represent the surviving elements of the ventral paired aortae. The internal carotid arteries are derived from the third arches and the persisting cephalic portions of the original dorsal paired aortae. The sections of the dorsal aortae which lie between the third and fourth arches disappear. The proximal portion of the right ventral aorta becomes the right innominate artery. The subclavian artery on that side is derived from the fourth right arch, a persisting segment of the right dorsal aorta, and usually the sixth intersegmental artery. On the left, the fourth arch becomes the definitive aortic arch which continues as the descending aorta. The pulmonary arteries are derived from the proximal portions of the sixth arches and their branches. Only on the left does the distal half of the sixth arch persist. This becomes the ductus arteriosus. When the truncus arteriosus divides sagittally, the pulmonary and aortic systems become separated. All arches not mentioned disappear completely.

Before the primitive dorsal aortae fuse, each gives off about thirty dorsal branches. With the union of these aortae the development of posterior paired vessels can be appreciated. These are arranged between the somatic segments and are designated as intersegmental arteries. Some of them later disappear while the remainder form the main stems of the lumbar, intercostal, and subclavian arteries. It should be noted that the sixth intersegmental arteries are usually incorporated in the subclavian arteries on both sides.

With the above information as a background, the embryology of our case can be explained briefly (Fig 6). The right fourth aortic arch persisted in entirety and became the main blood conveyor to the descending aorta. The left fourth arch also remained and thus a permanent vascular ring about the esophagus and trachea was formed. The extremely unusual feature in this anomaly was the survival of the primitive left dorsal aorta between the third and fourth arches. From this arose the first intersegmental artery which ultimately became the first portion of the left subclavian system (Fig 7). Due to another rare coincidence, this persistent dorsal aortic segment also became the sole supplier of blood to the left side of the head. This resulted from an atresia of the left ventral aorta between the third and fourth arches. The development of a left innominate artery is therefore explained.

*CASE 2*—A F, a 9 month old male, came to the hospital for the first time in October, 1942, because of cough first noticed at the age of two weeks.

*Past History*—The child was born at term by cesarean section. His birth weight was 7½ pounds. There was no neonatal distress, jaundice, or cyanosis. He was formula fed from the start, received adequate vitamins, and gained well.

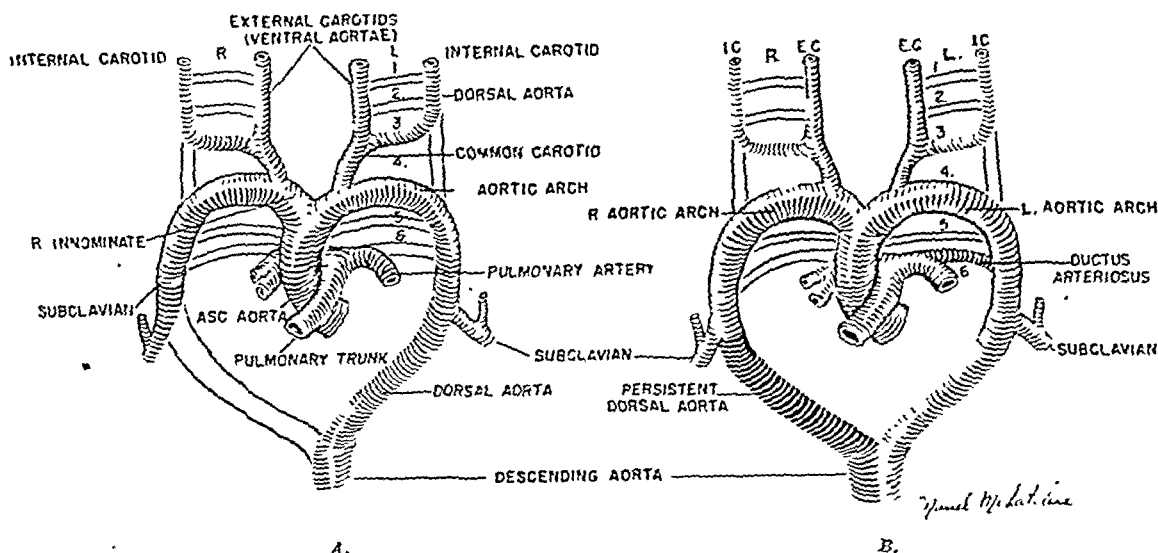


Fig. 5.—A, diagram showing the normal development of the great vessels about the heart (see text). B, arrangement of the embryonic vessels in the most common type of double aorta. A patent ductus arteriosus is often found with this type of anomaly.

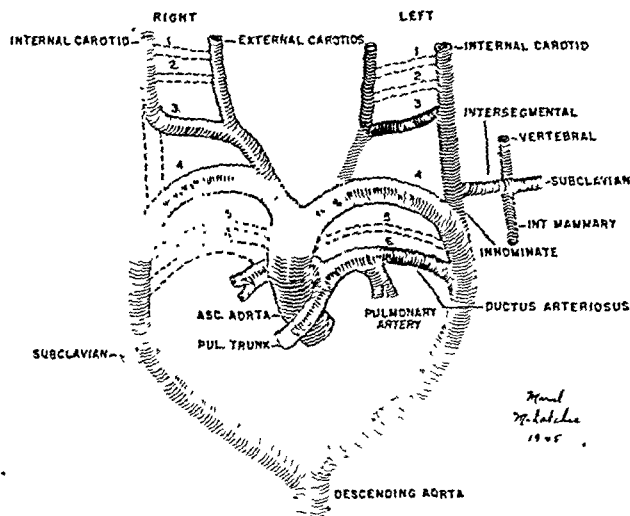


Fig. 6.

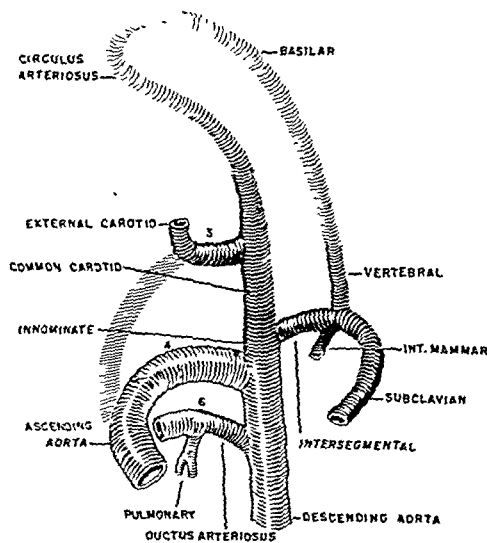


Fig. 7.

Fig. 6.—Diagrammatic ventral view of aortic system in Case 1 to show the embryonic development of the great vessels (see text).

Fig. 7.—Lateral view of the left innominate artery in Case 1 (see text).



At the time the child was discharged from the maternity hospital, his mother noticed that he had a persistent loose cough which was most noticeable at night and in the morning. Two weeks before he was brought to the hospital the baby's cough became worse. He started to vomit part of his formula after each feeding.

*Physical Examination.*—The child was well developed and somewhat obese. He breathed noisily and had a continuous loose cough. The throat was diffusely injected and there was a moderate amount of mucus in the pharynx. The chest expanded equally. There was a mild degree of funnel chest. The percussion note was not impaired. On auscultation, musical and coarse râles were heard over both lung fields.

He weighed 19 pounds. His temperature was 99.8° F., respirations 36, pulse 100. The blood pressure was 85/50. The remainder of the physical examination was not remarkable.

Bronchoscopic examination revealed a normal appearing larynx, trachea, and bronchi. No foreign body was seen.

*Laboratory Data.*—The Hinton test was negative, the tuberculin test 1:1,000 was negative, and the urine was negative. The white blood cell count was 13,000, with normal differential; the red blood cell count was 4.3 million, and hemoglobin was 13.5 Gm. per 100 c.c.

Roentgenogram of the chest revealed a prominence of the upper mediastinal shadow on the right.

*Course.*—The infant was quite uncomfortable during his hospital stay. He coughed frequently, especially during and after feedings. Following the bronchoscopy, his temperature rose to 104° F. and he developed a purulent left otitis media. This infection responded well to sulfadiazine, and his temperature returned to normal within three days. The child was discharged to be followed in the Outpatient Department.

*Second Admission.*—The patient returned to the hospital two weeks later with a chief complaint of fever and cough. His mother stated that the child was vomiting most of his feedings. He was found to have a pneumonia of the left lower lobe which responded to sulfadiazine.

*Course.*—During the next fourteen months the patient returned frequently to the Outpatient Department. He developed another attack of purulent otitis media of the left ear, but otherwise did well. However, his cough persisted off and on, and it was noted that he had a slight wheeze when he became excited. The depression of the sternum progressed somewhat. X-rays of the chest showed no appreciable changes.

*Third Admission.*—On Feb. 18, 1944, at the age of 2 years, the child was brought to the hospital again with a chief complaint of more pronounced cough and fever of approximately three weeks' duration. He had vomited after most of the coughing paroxysms and had lost approximately three pounds.

The child was fairly well developed but looked pale. He weighed 24½ pounds. His temperature was 99.6° F., pulse 132, and blood pressure 88/60. He had a peculiar gagging cough which appeared to be productive. The throat was diffusely injected. The trachea was shifted to the right. The chest was hyperresonant to percussion. There were numerous squeaks, groans, and râles, particularly over the right lower lobe posteriorly. The funnel chest was present as before. No heart murmurs were noted. The remainder of the physical examination was essentially negative.

The white blood cell count was 33,000 with 75 per cent polymorphonuclear cells, red blood cell count was 4.8 million, hemoglobin, 15 Gm. per 100 c.c. Tuberculin test 1:100 was negative.

Roentgenogram of the chest showed no change from the previous examinations. The question of a right-sided aorta was considered. Consequently, a barium swallow was done which confirmed the previous findings of displacement of the superior mediastinum to the right. But it also showed narrowing of the trachea at the level of the aortic arch posteriorly and on the right, probably due to pressure. The arch of the aorta appeared to be in normal position. A right-sided arch could not be definitely excluded, but in such an event it would have to be a double aorta encircling the esophagus and trachea. The lung fields had not changed in appearance since the last observation nor had the funnel-chest deformity.

*Course.*—The child's upper respiratory infection subsided after treatment with sulfadiazine. Broncho-scopy was performed, but so much secretion was encountered that it was difficult to see the bronchi. Lipiodol was injected, but the amount was insufficient to give good pictures.

Twenty-four hours following the bronchoscopy, the child developed marked respiratory distress. Only temporary relief was afforded by bronchoscopic aspiration of the excessive mucus; therefore, a tracheotomy was done.

The child continued to have respiratory distress and ran a temperature up to 103° F. On the twelfth day after the operation, an esophagotracheal fistula developed. Administration of fluids by mouth was stopped and a gastro-tomy was performed. Administration of sulfadiazine was continued. An adequate caloric intake was maintained through the gastro-tomy.

At the end of four months the esophagotracheal fistula had healed, the tracheotomy tube was out, the gastrostomy wound had healed, and the child was discharged to a convalescent home.

He was seen on several occasions in the Outpatient Clinic and the parents insisted that he was quite well, though he continued to cough intermittently and to have some recurring upper respiratory infection. No mention was made of distress on feeding.

A roentgenogram in June, 1945, revealed very little change in the appearance of the chest.

*Fourth Admission.*—The child was readmitted to the hospital in January, 1946. He was then 4 years old. He was able to eat only liquids or strained foods and even with these he vomited two or three times at mealtime. His mother had not noticed any cyanosis. She admitted that he wheezed audibly when excited. He had had frequent upper respiratory infections from which recovery was slow.

The child was 39 inches in height and weighed 37 pounds. His blood pressure was 110/50. He had a marked funnel chest deformity. The teeth were badly decayed. There were well-healed gastrostomy and tracheotomy wounds. There was inspiratory retraction of the sternum when he was excited. A systolic murmur was heard one inch to the left of the sternum. This was transmitted to the left axilla and was best heard to the left of the sternum between the second and third interspace. Femoral pulses were present. Examination of the lungs was not remarkable.

Roentgen examination and x-ray films confirmed the previous impression of a vascular ring encircling the trachea and esophagus. A barium swallow showed a characteristic picture of a double arch of the aorta. The esophagus at this level was seen to be deformed both posteriorly and anteriorly due to compression. The trachea at this level was slightly narrowed and displaced anteriorly.

*Operative Findings and Procedure.*—On Jan. 21, 1946, a left thoracotomy was performed under intratracheal, oxygen ether anesthesia.

After the mediastinal pleura was retracted from the great vessels and the base of the heart, an ascending aorta of normal calibre was seen to leave the heart at its usual site. It passed in front and to the left of the trachea into the posterior mediastinum. Two branches arose from it which were identified as the left common carotid and subclavian arteries (Fig. 8, A). Instead of following its usual course down the left thoracic gutter, the aorta curved behind the esophagus and into the right chest. It was obvious that surgical division of the vascular ring could be performed only through a right thoracotomy incision. The wound was closed and the child was returned to the ward pending further surgery through the right side.

A second operation was performed on Feb. 13, 1946, and a right posterolateral thoracotomy incision was made. The pleura was entered through the fifth intercostal space. The apex of the lung was retracted downward and the azygos vein was doubly ligated and divided. The highest intercostal vein was dealt with similarly. This was necessary to obtain adequate exposure of the arteries in question (Fig. 8, B).

The most prominent structure first noticed was the aorta emerging from behind the esophagus at a slightly lower level than it was seen to disappear on the left side. It descended down the thorax along the right lateral margin of the vertebral column, curving gently to the left at its distal end so that it went through the diaphragm in the midline. At the angle where the aortic arch became the descending aorta, a large artery came off and ascended to the apex of the thorax. This was an innominate artery which branched into the right common carotid and right subclavian.

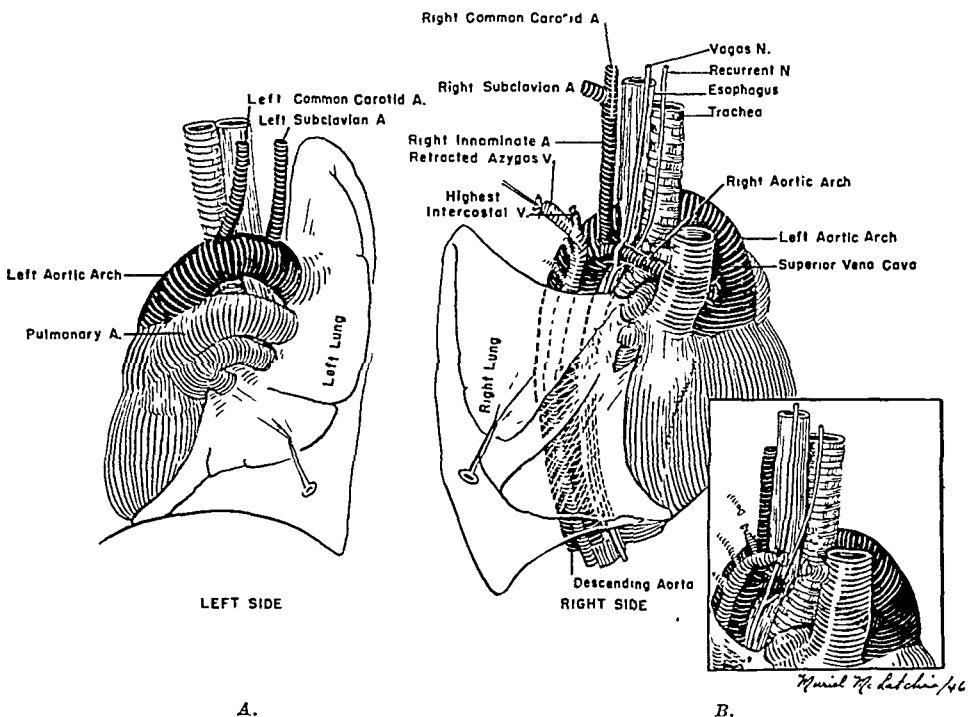


Fig. 8.—Diagram illustrating the anatomy found in Case 2. A, View from the left; B, view from the right. Inset: After division of the right or ventral arch.

As the mediastinal structures were further dissected, a vessel connecting the ascending and descending portions of the aorta came into view. It arose from the ascending aorta just above the base of the heart and traversed the left posterolateral border of the superior vena cava. It then coursed dorsally, slightly superiorly, and to the right, passing over the first portion of the right main bronchus at its origin from the trachea. It joined the descending aorta at the level where the right innominate artery arose. The diameter of this vessel was about one-eighth that of the aorta. There was no doubt that this represented a persistent right fourth aortic arch. A definite groove in the surface of the right main bronchus could be palpated where it passed over and in front of that structure. Since this segment of the vascular ring about the esophagus and trachea was superfluous as a blood conveyer, it was doubly ligated with silk ties and divided. The ligated ends of this vessel separated immediately after division (Fig. 8 inset).

No ductus arteriosus or ligamentum was found on the right. The vagus nerve on that side descended in front of the right aortic arch. The left recurrent laryngeal nerve branched from the vagus just caudad to the arch, coursing beneath and behind it to ascend along its usual course. The operation was finished in the routine manner.

**Postoperative Course.**—Recovery from operation was uneventful save for a tachycardia which persisted for several weeks but gradually subsided.

*Embryologic Considerations.*—It is interesting to note that the early embryonic arrangement of the aortic arch vessels was apparently a mirror image of the vascular pattern in Case 1. Contrary to Case 1, there was an innominate artery on the right side, and the two surviving vessels on the left became the common carotid and subclavian arteries. The reversal of laterality of these vessels can be appreciated on comparing Figs. 6 and 13, A. The evolution of the left aortic arch system was normal except for the failure of the distal half of the sixth arch to appear. As a result, there was neither a patent ductus arteriosus nor ligamentum on that side. This will be more fully discussed below. The left fourth arch became the largest vessel leaving the heart.

The abnormal development of the right arch system led to the ultimate anomalous arrangement of the great vessels. The right ventral aorta between the third and fourth arches disappeared, whereas the segment of the right dorsal aorta between these arches survived (Fig. 13, A). The first intersegmental artery connected with this segment and later became the first portion of the right subclavian artery. Because of this disposition of embryonic vessels, an anomalous right innominate artery resulted.

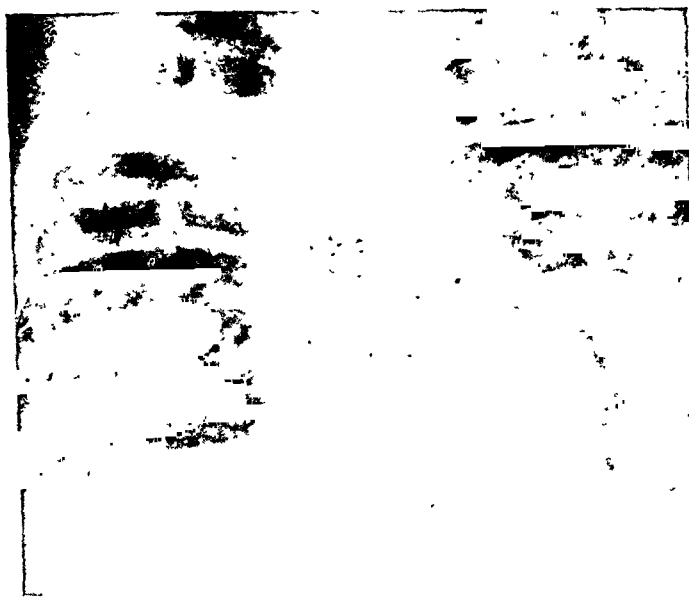


Fig. 9.—Case 2. Chest film showing partial collapse of the right upper lobe and abnormal arrangement of the structures at the base of the heart. Arrow indicates shadow caused by a right-sided descending aorta.

Normally, the right primitive dorsal aorta disappears between the origin of the sixth intersegmental artery and its fusion with the left dorsal aorta (Fig. 5, A). In this case, the right dorsal aorta persisted in its entirety (Fig. 13, A). Although that portion distal to the right fourth arch remained patent as a vessel, it failed to lengthen with growth of the embryo. With the origin of the right innominate artery acting as a fixed point, the left dorsal aorta was drawn gradually to the right. This vascular shift led to the final placement of the descending aorta on the right. An attempt has been made to show this diagrammatically (Fig. 13, B and C).

The occurrence described above caused part of the left fourth aortic arch and left dorsal aorta to lie behind the esophagus. The persistent right fourth arch remained to pass in front of the trachea and connect the ascending and descending aortae. A vascular ring about the trachea and esophagus was formed in this manner. Although a ductus arteriosus or its remnants were carefully looked for at both operations, neither was found on the right

• or on the left. This would indicate that there was never any connection between the pulmonary and arterial vascular systems via the distal portions of either sixth arch. It seems probable, therefore, that during fetal life there was a shunt between the venous and arterial vascular beds through the interauricular or interventricular septa. The septal defect most likely closed shortly after birth since no characteristic cardiac murmur has ever been heard.

#### DISCUSSION

Respiratory stridor in infancy is a frequent complaint and may be due to a variety of causes. There is often considerable confusion concerning its etiology. In some cases it is due to an abnormality of the larynx such as a deformity or flaccidity of the epiglottis, arytenoids, or aryepiglottic folds. In these, the onset is usually at birth. Respiratory distress may be absent or quite appreciable. Direct laryngoscopy will establish the diagnosis.

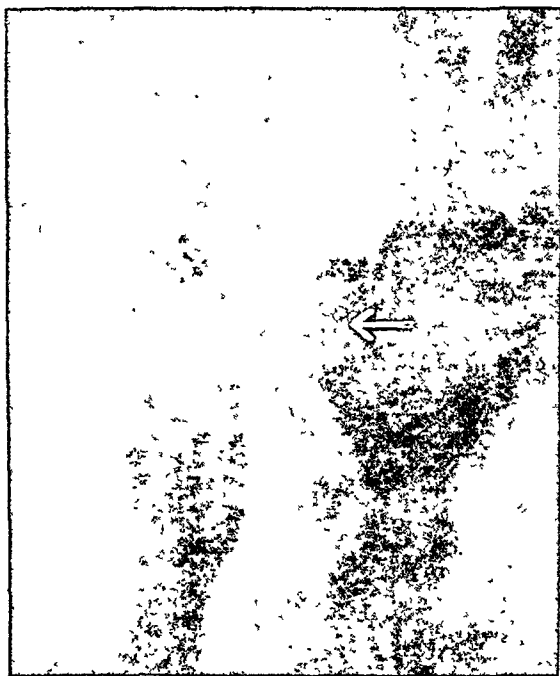


Fig. 10.—Case 2. Posteroanterior view of barium-filled esophagus. Note the reversal of the esophageal deformity as compared with that of Case 1. Arrow points to lateral impression of esophagus by the left aortic arch

An inspiratory stridor may occur in tetany neonatorum. Usually, there will be other clinical signs. The presence of low serum calcium and elevated serum inorganic phosphorus concentrations with normal serum nonprotein nitrogen and no significant renal insufficiency are characteristic of this diagnosis. Likewise, in idiopathic hypoparathyroidism, these determinations will establish the diagnosis. Laryngeal stridor or crow may also occur in the tetany of healing rickets. In some cases of cerebral damage, stridor is an outstanding sign.

Other causes of inspiratory stridor are the presence of a foreign body in a bronchus, pressure from tuberculosis of the peribronchial lymph nodes, or congenital heart disease. The history, physical examination, x-ray examinations of the chest, and tuberculin tests are helpful in arriving at a diagnosis in such cases.



Fig. 11.

Fig. 12.

Fig 11—Case 2 Lateral view of esophagus following a barium swallow. Arrows indicate posterior indentation of esophagus and anterior impression of the trachea.

Fig. 12—Right anterior oblique view of chest and abdomen to demonstrate the entire barium-filled esophagus with its deformity. Note moderate dilatation of esophagus proximal to the constriction and the descending aorta on the right side. Arrows point to the descending aorta.

Congenital atresia of the posterior choanae, in which the presenting symptoms are a peculiar click on inspiration, marked respiratory difficulty, and cyanosis especially during feeding, may cause stridor. This condition can be diagnosed easily by the detection of obstruction to the passage of a catheter from the nose into the pharynx.

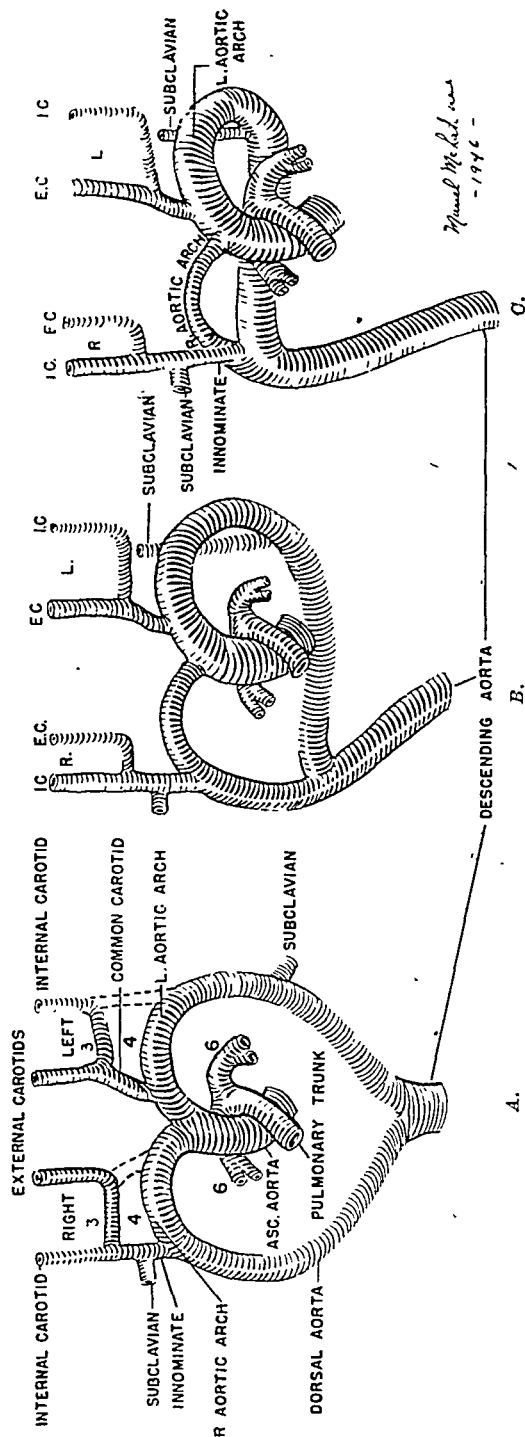


Fig. 13.—4. the arrangement of embryonic vessels in Case 2. Note that this is a mirror image of Case 1 except that the distal segments of the sixth arches failed to appear. B and C show the development of a right descending aorta due to the failure of the persistent right dorsal aorta to lengthen.

In the past, a large number of cases of inspiratory stridor have been attributed to an enlarged thymus. It may be that a large thymus was the cause of respiratory difficulty in a few patients, but it is probable that the thymus was accused wrongly in the majority of cases. A persistent right aortic arch may give the same widening of the upper mediastinum by x-ray as the enlarged thymus. It is possible that some cases of inspiratory stridor which were attributed to an enlarged thymus were really due to an anomalous aortic vascular ring with a large right aortic arch.

In cases where constriction by an anomalous ring composed of a double aortic arch is found, the stridor is usually noticed at birth. Wheezy respiration and attacks of coughing are frequently observed,<sup>11</sup> and the coughing and stridor often become worse when the infant is fed.<sup>14</sup> In many cases it is noted that the infant breathes normally while asleep.

In all cases, the respiratory signs are markedly aggravated by upper respiratory infections.<sup>7, 8</sup> In some instances the respiratory distress is so great as a result of these infections that a tracheotomy has been performed without effect. These children are unusually susceptible to such infections. Repeated pulmonary infections have ultimately led to fatalities in many cases.<sup>17</sup>

As pointed out by Faber and associates,<sup>7</sup> in infants and children with a double aortic arch, noisy breathing appears to be a much more common complaint than dysphagia. Dysphagia is frequently a minor symptom during the first few months while the child is on a liquid diet. As a more solid diet is given, this symptom becomes more pronounced.

Associated cardiac anomalies occur<sup>2</sup> comparatively rarely. Usually, these infants do not have other congenital abnormalities.<sup>16</sup>

*Diagnosis of Double Aortic Arch.*—The observation of respiratory wheezing or stridor even without dysphagia which is aggravated by deglutition should make one suspect the presence of a double aortic arch.

A plain posteroanterior roentgenogram of the chest may arouse suspicion of anomalous great vessels about the heart because of a widened mediastinal shadow extending mostly to the right. Often the normal aortic knob is not seen on the left. Left and right oblique views may show the aorta ascending on the right and passing behind the esophagus respectively.<sup>2</sup>

The most informative special examination is that of the esophagus following the ingestion of barium. The lateral surface of this structure is indented by the aortic arch which carries the major blood load. The defect can occur on either side as illustrated by Figs. 2 and 10. In Case 1, the largest fourth aortic arch and the lateral esophageal indentation on the right. The converse was true in Case 2. A similar defect is also seen posteriorly at the site of the retroesophageal aorta.

Sometimes there may be forward and lateral displacement of the trachea and esophagus. They have been noted to be displaced to the left by right aortic arches.<sup>2</sup> Gross<sup>3</sup> and Neuhauser<sup>12</sup> point out that narrowing of the trachea at the site of the constricting vascular ring is a prominent feature. This is best illustrated by bronchography, although it may be seen adequately with plain chest



films. If the above tracheal and esophageal deformities are noted, esophagoscopy is an unwise procedure, because of the danger of perforation.

*Surgical Approach.*—It is most important for the surgeon to know which side of the chest he should enter to correct this lesion. A study of previously reported cases suggests that a left chest approach is the wisest in most instances.<sup>3</sup> This is because the surviving left fourth arch is usually more amenable to division, since the right aortic arch almost always conveys most of the arterial blood. The development of the aortic arch system, however, is so complex that it is potentially subject to many variations. As more of these anomalies are studied, hitherto unreported vascular arrangements probably will be brought to light. The surgeon must, therefore, be careful to choose the correct side of the chest through which to operate.

The cases presented here may be helpful in selecting the accurate surgical approach. If the posterior and right lateral aspects of the esophagus are indented by the larger persistent right aortic arch (Fig. 2), the lesser aortic arch, which is the vessel to be divided, will be found on the left anterolateral aspect of the mediastinum. The visualization of the main aorta descending down the left side of the vertebral column (Fig. 4) would corroborate this probability. Obviously, under these conditions, the vessel to be chosen for ligation will be best reached through the left pleural cavity. Case 1 illustrates this combination of x-ray findings. As previously emphasized, Case 2 is a mirror image of Case 1. Here there were defects of the left lateral and posterior surfaces of the esophagus (Figs. 10 and 11) caused by the larger left aortic arch. The descending aorta was seen by x-ray in the right chest (Fig. 12). As stated in the operative report of Case 2, the anomalous, smaller, right arch could be reached only through the right chest. In summary, when an annular double aortic arch about the trachea and esophagus is suspected, the lateral esophageal deformity and the location of the descending aorta should be helpful findings in deciding which pleural cavity is to be entered.

*Conclusion.*—Patients with symptoms caused by this congenital anomaly should be operated upon. It is true that this lesion has been found at autopsy in elderly individuals who have never had dysphagia or respiratory distress.<sup>3, 6</sup> As Blackford and associates<sup>4</sup> point out, however, it is conceivable that arteriosclerotic or hypertensive changes in later life may initiate a symptom complex. One should, therefore, consider the desirability of operation early in life even in the absence of symptoms.

Grateful acknowledgment is made to Dr. John L. Bremer for his invaluable assistance with the embryologic aspects of these cases and to Dr. Laurence L. Robbins for his interpretations of the roentgenologic studies in each.

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# PENICILLIN IN TREATMENT OF DIPHTHERIA AND DIPHTHERIA CARRIERS

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FLEMING,<sup>1</sup> in 1929 and in 1932,<sup>2</sup> and subsequently Chain and associates,<sup>3</sup> demonstrated that penicillin inhibited the growth of *Corynebacterium diphtheriae* in vitro. These observations, plus the successful inhibition of the growth of *C. diphtheriae* in infected guinea pigs,<sup>4</sup> suggested the clinical application of penicillin to the treatment of both persons acutely ill with diphtheria and convalescent carriers. The results were very encouraging in the treatment of the first group, five convalescent carriers and six patients with faucial diphtheria.<sup>5</sup> However, this limited experience left many questions unanswered. It was necessary to determine the most suitable dosage and route of administration, the duration of treatment, its effect on complications due to diphtheria toxin and secondary invaders, and, above all, whether or not penicillin was regularly effective and to what extent it could be relied upon.

The presence of diphtheria among prisoners of war and among American soldiers in one of the base sectors of the European Theater of Operations in the autumn and winter of 1944 afforded the opportunity to investigate these problems. The study was undertaken simultaneously in five hospitals. The data here reported are the composite results of observations made in the hospitals concerned.

## OUTLINE OF STUDY

1. It was stressed that penicillin is not a substitute for antitoxin and should not be used as such. This was based upon previous laboratory observations.

2. All patients suspected of having diphtheria were to receive 40,000 units of antitoxin intramuscularly. If indicated clinically, an additional 20,000 units might be given intravenously and larger doses of antitoxin might be given if considered necessary.

3. All patients with diphtheria, except those seen at the Two Hundred Thirty-Fifth General Hospital, were to have penicillin, to be begun after a throat culture was taken but without waiting for the laboratory report.

The penicillin dosage and manner of administration suggested were as follows:

*Forty-Third General Hospital.*—20,000 units intramuscularly every three hours.

*Prisoner of War Hospital (8277).*—20,000 units intramuscularly every two hours.

*Prisoner of War Hospital (8276).*—Spraying of nose and throat every hour during the day and every three hours at night with penicillin solution (1,000 units per milliliter of physiological sodium chloride solution).

*Third General Hospital.*—20,000 units intramuscularly every three hours, plus spraying of the nose and throat every hour for the first day and every three hours thereafter day and night.

*Two Hundred Thirty-Fifth General Hospital.*—The patients were to receive antitoxin and to serve as controls.

4. Patients were to receive penicillin until three, daily, consecutive, throat cultures were negative. Thereafter, cultures were to be taken daily for three days, every second day for six days, and every third day for nine days. If all of these were negative, the patient was to be considered free of *C. diphtheriae*.

5. The virulence and type of the bacteria isolated from each patient were to be determined.

#### METHODS AND MATERIALS

Direct smears of the throat or other lesions were made on admission. At the same time, swabs with material from the diseased areas were inoculated on Loeffler's serum agar and incubated for from eighteen to twenty-four hours. Suspicious organisms found on the direct smear were reported as such, but a definite diagnosis of diphtheria was not made at this time. Patients with typical lesions containing organisms morphologically similar to *C. diphtheriae* were treated with antitoxin. After eighteen to twenty-four hours, all Loeffler cultures were smeared on glass slides, stained with alkaline methylene blue or Neisser's stain, and examined. Frequently, a positive diagnosis could be made from this original culture. Occasionally, however, the morphologically typical beaded and banded rods were absent and it was necessary to subculture before a positive diagnosis could be made. All Loeffler cultures were streaked onto tellurite chocolate agar and blood agar plates. From the latter, concomitant beta hemolytic streptococcus infection could be determined. Typical colonies of *C. diphtheriae*, appearing as dull, somewhat rounded, gray-black, butyraceous colonies and consisting of gram-positive rods, were picked and subcultured on Loeffler's serum agar. After twenty-four hours of incubation these cultures were again examined and if morphologically characteristic of *C. diphtheriae* they were transplanted to three, semisolid, tryptose phosphate agar media containing dextrose, sucrose, and dextrin, respectively. This semisolid agar maintained as good a growth of *C. diphtheriae* as the common Hiss serum water which was likewise used toward the latter part of the experiment and was easier to prepare. All sucrose fermenters were discarded and reported as diphtheroids. It was found that all *C. diphtheriae* fermented dextrose and dextrin in from twenty-four to forty-eight hours, and a positive diagnosis of *C. diphtheriae* could be and was made at this time.

Because of the scarcity of animals, cultures were accumulated until at least six to ten were available and the pure Loeffler cultures were subcultured on tryptose agar. After eighteen hours the growth was washed down with sterile saline, the mixture diluted to a nephelometer reading of 3, and this mixture used for the virulence tests. Either rabbits or guinea pigs were used. The method used was as follows: The dorsum of the animal was shaved the day before the test. The shaved area was marked off into blocks with indelible pencil, each

block containing 0.1 c.c. of the nephelometer culture mixture. As many as ten virulence tests could be done on one animal. Five hours after the initial injections, the animal received 1,000 units of diphtheria antitoxin intravenously. One-half hour later, 0.1 c.c. of the culture-saline mixture, kept in the refrigerator since its preparation, was injected on the opposite shaved site of the animals to serve as controls. In from three to five days these virulence tests were read. All virulent cultures resulted in necrosis of the area of injection. Nonvirulent organisms caused only a slight redness for twenty-four to forty-eight hours, which rapidly disappeared. All cultures of the throat yielding *C. diphtheriae* gave positive virulence tests.

Identification of the type of strain of *C. diphtheriae* was not attempted at the time. Subsequent examinations of all available stock cultures revealed that all but two, which were of a gravis strain, belonged to the mitis type of *C. diphtheriae*. Virulence tests were performed on all strains isolated from patients at the Third General Hospital and in about 50 per cent of the cases from other hospitals concerned. Cases with avirulent strains were excluded from this survey.

The prevailing wartime conditions prevented close adherence to the program outlined in some hospitals. At the Two Hundred Thirty-Fifth General Hospital, because of the need for ward space, the control patients who remained carriers for thirty days were treated with penicillin. Twenty persons with faucial diphtheria admitted thereafter were treated with intramuscular penicillin. Transfer of patients interrupted the continuity of the observations. Transfer of personnel concerned with the investigation interfered with the case records and limited the amount of laboratory work.

Thus the original plan was modified to comply with existing conditions. Nevertheless, eighty patients with faucial diphtheria were carefully observed and will serve for the evaluation of the efficacy of penicillin in diphtheria. Forty-two patients with faucial diphtheria were treated with antitoxin alone and served as controls, and thirty-five convalescent carriers were treated with penicillin administered intramuscularly locally, or both ways.

### *Faucial Diphtheria.*—

### RESULTS

*Local Penicillin:* Penicillin in the form of a nose and throat spray of 1,000 units per milliliter of physiologic saline solution was administered every hour during the day and every three hours at night for seven days to twenty-one patients. Only two of the twenty-one patients became negative for *C. diphtheriae* within that period.

*Intramuscular Penicillin:* Comparison of results of the eighty penicillin treated patients with the control group (see Figs. 1 and 2 and Tables I and II) reveals that at five days after onset of the disease the percentage of positive throat cultures among the penicillin treated patients was 27.5 per cent, 100 per cent for forty-two controls, and 83 per cent for the 457 reported by Hartley and Martin<sup>6</sup>; at ten days, positive cultures were obtained from 7.5 per cent, 92.8

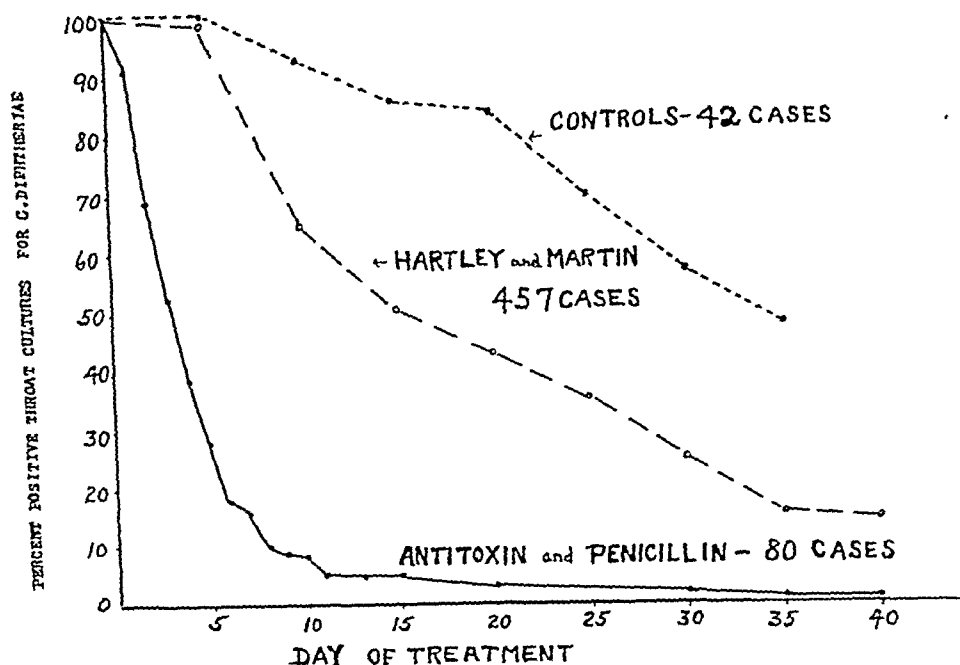


Fig. 1.—Comparison of the results obtained in the treatment of diphtheria with antitoxin alone and with penicillin plus antitoxin.

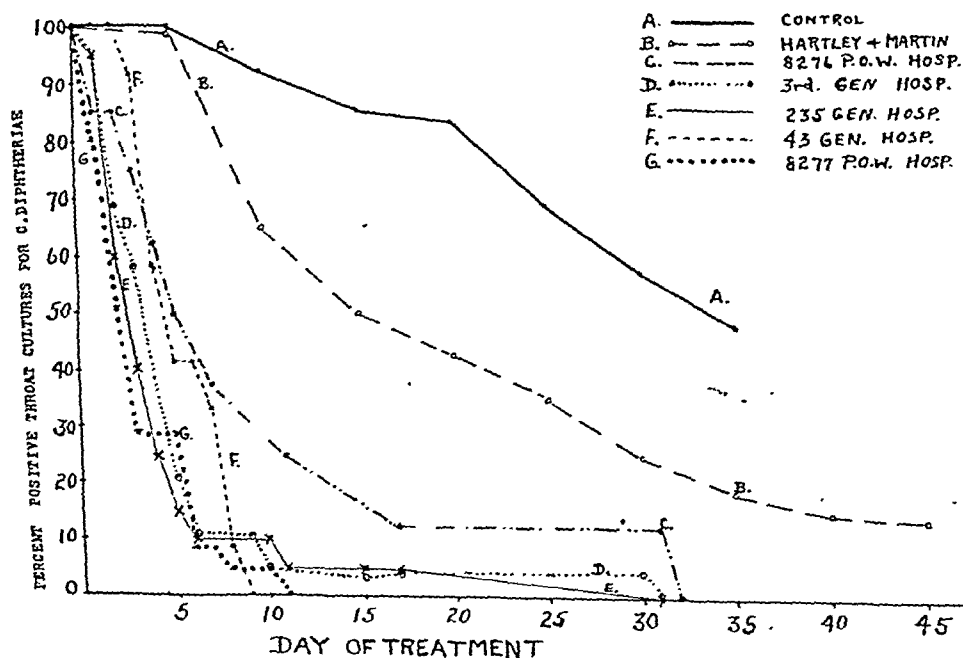


Fig. 2.—Comparison of the results obtained in the treatment of diphtheria with antitoxin alone and with penicillin plus antitoxin in each of the five hospitals.

TABLE I. DURATION OF POSITIVE NOSE AND THROAT CULTURES FOR *C. Diphtheriae* IN CASES OF FAUCIAL DIPHTHERIA TREATED WITH PENICILLIN AND ANTITOXIN AT THE VARIOUS HOSPITALS

DAYS	POSITIVE CULTURES IN EACH HOSPITAL										TOTAL POSITIVE CULTURES (80 CASES)	
	43 G.H. (12 CASES)		235 G.H. (20 CASES)		3 G.H. (19 CASES)		8276 P.O.W. (8 CASES)		8277 P.O.W. (21 CASES)			
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
1	12	100	19	95	18	94.7	7	87.5	17	80.9	73	91.25
2	12	100	12	60	13	68.4	7	87.5	11	52.4	55	68.75
3	11	91.6	8	40	11	57.9	6	75	6	28.6	42	52.50
4	7	58.3	5	25	8	42.1	5	62.5	6	28.6	38	38.75
5	5	41.6	3	15	4	21.0	4	50.0	6	28.6	22	27.50
6	5	41.6	2	10	2	10.5	3	37.5	2	9.5	14	17.50
7	4	33.3	2	10	2	10.5	3	37.5	2	9.5	13	16.25
8	1	8.3	2	10	2	10.5	2	25.0	1	4.8	8	10.00
9	0	0	2	10	2	10.5	2	25.0	1	4.8	7	8.75
10			2	10	1	5.2	2	25.0	1	4.8	6	7.50
11			1	5	1	5.2	2	25.0	0	0	4	5.00
17			1	5	1	5.2	1	12.5			3	3.25
31			0	0	0	0	1	12.5			2	2.5
32							1	12.5			2	2.5
77							0	0			0	0

TABLE II. RATE OF DISAPPEARANCE OF *C. Diphtheriae* IN PATIENTS TREATED WITH ANTITOXIN AND WITHOUT PENICILLIN (42 CASES)

PATIENTS WITH POSITIVE NOSE OR THROAT CULTURE

DAYS	3 G. H.		235 G. H.		TOTAL		HARTLEY AND MARTIN (457 CASES)
	NO.	%	NO.	%	NO.	%	%
5	18	100	24	100	42	100	100
10	18	100	21	87.5	39	92.8	65
15	17	94.4	19	79.1	36	85.7	50
20	17	94.4	18	75	35	83.3	43
25	15	83.3	14	58.3	29	69.0	35
30	14	77.7	10	41.6	24	57.1	25
35	12	66.6	8*	33.3	20	47.6	18
40	10	55.5					15
45	9	50.0					
50	9	50.0					8
55	8	44.4					
60	5	27.7					7
65	4	22.2					
over 65	2*	11.1					6

\*Treated with penicillin as a convalescent carrier.

per cent, and 65 per cent respectively. At fifteen days, less than 5 per cent of the penicillin treated patients remained positive, against 85.7 per cent for our controls and 50 per cent for the patients reported by Hartley and Martin.<sup>6</sup> Thus penicillin affected a considerable reduction in the period of infection with *C. Diphtheriae*. The results were similar in each of the five hospitals.

*Treatment of Carrier State.*—

*Local Penicillin:* At the Two Hundred Thirty-Fifth General Hospital, eight patients who were convalescent carriers for from twenty-six to thirty days were given penicillin nose drops every three hours for seven days. All ceased to be carriers within seven days.

In another hospital where the patients had been carriers for a longer time and had previously been treated with intramuscular penicillin, only two of thirteen were cleared of *C. diphtheriae* during the seven- to twenty-three-day period of local therapy.

*Intramuscular Penicillin:* Intramuscular penicillin, 20,000 units every three hours, terminated the carrier state within four days in six of the nine patients at Prisoner of War Hospital (8277), and with 15,000 to 20,000 units every three hours, four of five carriers treated at the third General Hospital became negative. Thus ten of fourteen carriers were cured with penicillin.

#### PENICILLIN TREATMENT OF CONVALESCENT CARRIERS OF *C. Diphtheriae*

##### *Local Penicillin.*—

*Two Hundred Thirty-Fifth General Hospital:* Eight patients, "convalescent carriers for from twenty-six to thirty days prior to treatment, received nose drops of penicillin\* saline solution every hour during the day and every three hours at night.

- 2 became negative 1 day after treatment was started
- 1 became negative 2 days after treatment was started
- 4 became negative 5 days after treatment was started
- 1 became negative 6 days after treatment was started

*Prisoner of War Hospital (8277):* Thirteen convalescent carriers,† some previously treated with penicillin unsuccessfully, received nose and throat spray of penicillin\* for from seven to twenty-three days.

- 1 became negative 7 days after treatment was started
- 1 became negative 11 days after treatment was started
- 11 remained carriers after treatment was discontinued.

##### *Intramuscular Penicillin.*—

*Prisoner of War Hospital (8277):* Nine convalescent carriers† received intramuscular penicillin 20,000 units every 3 hours. The average total amount injected was 1,540,000 units.

- 4 became negative 3 days after treatment was started
- 2 became negative 4 days after treatment was started
- 2 became negative 12 days after treatment was started
- 1 failed to respond to a total of 2 million units given in 12.5 days.

*Third General Hospital:* Five cases were treated with intramuscular penicillin, 15,000 to 20,000 units every three hours.

- 3 became negative 1 day after treatment was started
- 1 became negative 2 days after treatment was started, but recurred and was cleared by nasal spray
- 1 became negative 1 day after treatment was started, became positive again after 5 days, became negative after 740,000 units were given in 6 days then again became positive

#### *Effect of Penicillin on Course of Diphtheria and On Complications.*—

The diphtheritic membrane persisted for about the same length of time in the treated patients as in the controls. The faucial edema and the subjective feeling of soreness of the throat were, however, favorably influenced by penicillin.

\*A solution of 1,000 units of penicillin per milliliter of physiologic saline was used for nose drops and nasal spray.

†All patients had been carriers for at least thirty days prior to treatment with penicillin.



Although statistical data are not available, it was our impression that there was an appreciable clinical difference between the penicillin treated patients and the controls in the incidence and severity of complications due to pyogenic organisms. In the group treated with antitoxin alone, cervical adenitis was more commonly observed and persisted longer. Several patients with diphtheria had large peritonsillar swellings. These responded to penicillin. Three of these were suspected of being abscessed, but pus was not obtained on incision. These too cleared on penicillin therapy. Otitis media and clinical sinusitis likewise occurred among the controls but did not develop in the patients treated with penicillin. These conditions, if present on admission to the hospital, responded to penicillin therapy.

TABLE III. TOXIC COMPLICATIONS

CASE	SEVERITY OF DIPHTHERIA	ANTITOXIN		COMPLICATIONS	
		DOSAGE (UNITS)	DAY AD- MINISTERED	TIME OF APPEARANCE AFTER ANTI- TOXIN GIVEN	DESCRIPTION
Forty-Two Cases Treated With Diphtheria Antitoxin and No Penicillin					
1	Severe	40,000	5th	27 days 41 days 58 days	Palatal paralysis Myocarditis with bundle branch block Paralysis respiratory muscles including dia- phragm; died 58th day
2	Moderate	40,000	2nd	41 days	Polyneuritis
Forty Cases Treated With Penicillin and Diphtheria Antitoxin					
Penicillin 25,000 units every three hours					
3	Severe	150,000	5th	4th week	Palatal pareses; myo- carditis, moderate
4	Severe	80,000	4th	25th day 4th week	Myocarditis; moderate paresis, palate right side
5	Severe	100,000	5th	3rd week 24th day	Palatal paresis, tran- sient; more marked 6th week Myocarditis, mild
Penicillin 20,000 units every two hours					
6	Moderate	40,000	1st	4th week	Paralysis of accommoda- tion
7	Severe	100,000	8th	18th day	Palatal paralysis
8	Severe	60,000	6th	32nd day	Palatal paralysis
9	Severe	60,000	2nd	22nd day	Palatal paralysis

Toxic neurological and cardiac complications were observed in two of the forty-two control patients and in seven of the eighty treated with penicillin intramuscularly. Data on the twenty-one patients treated with penicillin spray are not available. Most of the neurological complications occurred in patients who came to the hospital between the third and eighth day of the disease, although there were a few such complications among those who were presumably admitted on the first or second day of their illness.

There were no deaths among the patients treated with penicillin and only one among the controls.

Special mention must be made of three patients who developed complications after intensive serum and penicillin therapy. In each the diphtheria was severe and the patients were admitted on the fourth, fifth, and sixth days of the disease. Because of the widespread membranes, the toxemia, and the severe cervical adenitis, large doses of antitoxin, 80,000, 100,000, and 150,000 units were administered, and penicillin was started immediately. In one instance, 40,000 units of penicillin were injected every three hours for the first three days, and 25,000 units every three hours thereafter. In the other two, 25,000 units were injected intramuscularly every three hours. In addition, penicillin was sprayed in the nose and throat every hour during the first day and every three hours thereafter. Even though these patients received intensive therapy and improved rapidly, each subsequently developed palatal paralysis and cardiac changes, and one developed peripheral neuritis. Once more these cases demonstrate the fact that penicillin is not a substitute for antitoxin.

Of a total of 157 patients with diphtheria, tonsils were present in 147, or 93.63 per cent. Of the carriers, thirty-five of forty-two, or 83.33 per cent, had tonsils. The tonsils were generally large, cryptic, irregular, and in many cases scarred. There seemed to be a clinical correlation between the persistence of the carrier state and the character of the tonsillar tissue present, but statistical data were not obtained. The patients most difficult to clear of *C. diphtheriae* were those whose tonsils were very large and cryptic. In one carrier in whom penicillin failed to eradicate the infection, tonsillectomy was successful. The tonsils of this patient on section yielded a pure culture of *C. diphtheriae*.

#### DISCUSSION

Ercoli and associates,<sup>7</sup> demonstrated that penicillin exerted a striking antibacterial effect on the bacteriemia produced in mice by the intraabdominal injection of a suspension of *C. diphtheriae* in mucin. They found penicillin to be ineffective in the toxemic infection of guinea pigs although it presumably prolonged the survival time by delaying the growth of the diphtheria bacilli. They suggested that, under the practical conditions of diphtheria in human beings, penicillin may be useful for its antibacterial effect, e.g., prophylaxis of exposed contacts, very early cases, and carriers; but they emphasized the importance of antitoxic treatment of active cases. Skinner<sup>8</sup> reported the favorable bacteriostatic effect of penicillin in the treatment of diphtheria patients and carriers. With a dosage of 100,000 units daily, eleven of fifteen patients were rendered free of *C. diphtheriae*, although smaller doses were less effective. Thrift<sup>9</sup> reported upon the favorable effect of penicillin used topically in clearing a persistent nasal carrier of *C. diphtheriae*.

These reports added to our data seem ample evidence that penicillin is an effective agent in the treatment of diphtheria, yet we were not invariably successful. With a dosage of 20,000 units every three hours injected intramuscularly, 7.5 per cent of our patients remained positive for *C. diphtheriae* after ten days of therapy. In one of the hospitals servicing prisoners of war, forty-six patients with diphtheria not included in our data had been treated

with penicillin. Some of these had had 20,000 units of penicillin every three hours intramuscularly for three or five consecutive days or a total of 480,000 and 800,000 units. Throat cultures taken fourteen days after the treatment was started were positive for more than 25 per cent of the patients, indicating that these dosages were inadequate or that the penicillin had not been continued long enough.

The dosage of penicillin administered to forty of our eighty patients with faucial diphtheria and to nine carriers was 20,000 units every three hours intramuscularly. The deviations from this dosage for patients with faucial diphtheria were 20,000 units every two hours for twenty-one patients, 25,000 units every three hours for six patients and 20,000 units every three hours accompanied by simultaneous spraying of the nose and throat with a saline solution of 1,000 units of penicillin per milliliter in thirteen cases.

The results in all groups were too similar (Fig. 2) and the groups too small to warrant conclusion as to which dosage was more effective. All dosages seemed adequate for most of the patients, provided that the penicillin was continued until three, consecutive, daily, negative cultures were obtained, and provided that penicillin was reinstituted immediately after the nose or throat culture reverted to positive. In such cases, penicillin was again administered until three consecutive daily negative cultures were obtained. Few patient's cultures became positive again after the second course of penicillin therapy.

Between 420,000 and 2,400,000 units of penicillin were needed to render the acute cases of faucial diphtheria negative. For convalescent carriers the total dose needed was generally less, although it necessitated up to 2,000,000 units in some instances.

It has been demonstrated by Ercoli<sup>7</sup> that a concentration of 1.25 to 1.5 units per milliliter, as measured by the cup test against *Staphylococcus aureus* number 20, completely inhibited the growth of stock strains of *C. diphtheriae*, while partial inhibition could be obtained in dilution of 0.35 unit per milliliter. This represents about 100 times the concentration effective against streptococci and pneumococci. Buxbaum and associates<sup>10</sup> found that over 50 per cent of 348 strains of *C. diphtheriae* were inhibited by a concentration of penicillin of 0.25 to 0.50 unit per milliliter, more than two thirds of the strains responded to 1 unit per milliliter, but some strains required 1.50, 2.0, and 4.0 units per milliliter, while few strains required 10 units for complete inhibition. Thus, larger doses of penicillin than have been used heretofore may be indicated for some of the strains. To attain a blood concentration of penicillin more than 1.0 unit per milliliter or high enough for most of the strains, 30,000 to 40,000 units should be injected intramuscularly every three hours.

The continuation of penicillin until three, consecutive, daily, negative, pharyngeal cultures were obtained seemed satisfactory, but there were recurrences of positive cultures in some of these cases within one to five days after penicillin was stopped. Penicillin immediately reinstituted in these cases and continued as in the first course of therapy was effective with rare exception. If, however, the second course of therapy was delayed for ten to fourteen days or longer, the results seemed less favorable. It was our impression that if a

third or fourth course of penicillin became necessary it became increasingly difficult to clear the patient of the infection. This raised the possibility that the particular strains of *C. diphtheriae* involved had acquired greater resistance to penicillin. Unfortunately, due to limited facilities, we were not able to decide this question at that time.

The criterion established for cure, nine, consecutive, negative, throat cultures within a period of eighteen days, was rigid. Had we accepted the usual three negative cultures on alternate days, some of the more stubborn infections would have been missed. More carriers would have been discharged, and the data for the efficacy of penicillin might have appeared better. Three or more negative cultures over a period of ten days would suffice, we believe, to eliminate most of the persistent carriers.

The data presented show definitely that in acute faucial diphtheria intramuscular penicillin was usually successful in eradicating the infection, whereas local therapy in form of a nose and throat spray of 1,000 units per milliliter failed in nineteen of twenty-one cases. In the convalescent carriers, local therapy seemed more successful in one hospital than in another. The results with local penicillin in the carriers are not convincing but are sufficiently encouraging to warrant further trial.

It has been suggested that penicillin be used prophylactically for susceptible exposed individuals. This procedure we believe must await much confirmatory data on the clinical effect of penicillin and a simpler procedure than repeated, three-hour, intramuscular injections of penicillin.

Penicillin has been recommended as a substitute for antitoxin in patients hypersensitive to horse serum. The incidence of complications among penicillin treated cases suggest that the withholding of antitoxin might prove to be a dangerous procedure. It would be justified if it were impossible to desensitize the patient for horse serum and if the possible harm anticipated from the antitoxic serum in a particular case were considered greater than that which might result from the effect of diphtheria toxin. Such cases are rare.

#### CONCLUSIONS

1. Patients with faucial diphtheria treated with antitoxin and penicillin, the latter injected intramuscularly every three hours until three, consecutive, daily, negative, nose and throat cultures were obtained, were rendered diphtheria negative more rapidly than were the patients who received antitoxin and no penicillin.
2. Carriers of virulent *C. diphtheriae* were likewise rendered free of the bacteria by treatment with penicillin.
3. Penicillin applied locally in the form of nose drops or as nasal spray was not effective in faucial diphtheria, but seemed more promising in the treatment of carriers.
4. Penicillin was ineffective in preventing toxic complications of diphtheria, but seemed to hasten the clearing and further the development of complications due to pyogenic organisms.
5. Penicillin should not be used as a substitute for diphtheria antitoxin.

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## STUDIES ON PERTUSSIS IMMUNIZATION

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I. *Immunization of Young Infants With Alum-Precipitated Pertussis Vaccine.*—As reported in a previous publication,<sup>1</sup> it was found that 75 per cent of infants below the age of 6 months developed agglutinins as a result of immunization with alum-precipitated pertussis vaccine. Young infants tolerated the vaccine extremely well, local reactions occurring in only 8.6 per cent and systemic reactions in 7.1 per cent. A follow-up study subsequent to immunization revealed that the incidence and severity of pertussis in those followed who had known exposure, familial or casual, were much less than in a similar group of nonimmunized urban clinic patients.

II. *Effect of Age on Agglutinin Response to Pertussis Immunization.*—The recommended three doses of alum-precipitated pertussis vaccine (40 billion per cubic centimeter, Lilly) were administered at monthly intervals to 8,690 Negro children from 2 weeks to 5 years of age. The agglutinin titers were run by the method of Miller and Silverberg<sup>2</sup> approximately two to four months following completion of immunization. The children were unselected except for the fact that their agglutinin titers were all negative prior to immunization.

The results show that infants below the age of 3 months developed agglutinins just as well as any age group (Tables I and II and Figs. 1 and 2). The total positive agglutination titers in infants below 3 months of age (92.10 per cent) was comparable to the 3- to 6-month age group and the 6- to 12-month group (94.39 per cent and 93.99 per cent respectively). Similarly, the strongly positive reactions in the 2-week to 3-month group (51.44 per cent) were as good as in any age group except the 18- to 24-month group, in which for some reason a large number developed high titers (67.59 per cent).

Some investigators<sup>3</sup> have found that young infants develop antibodies very poorly in response to pertussis vaccine. However, quantitative methods used by the earlier workers were ill adapted for the accurate assay of the antibodies concerned. Employment of a more adequate technique has resulted in many cases in the demonstration of antibodies. There is reason to believe, as will be shown later, that alum-precipitated pertussis vaccine is superior to fluid vaccine in the immunization of young infants. It has been repeatedly observed that some individuals do not have, or have a very poor capacity to produce antibodies. This has been attributed to inferior "antibody factories." This property, however, is not correlated with age as regards pertussis immunization, provided an appropriate vaccine is used. The capacity to produce pertussis antibodies is present in the young infant as in any other individual; the facility with which the antibodies are exfoliated into the blood stream of the infant may require a more prolonged antigenic stimulus such as is afforded by the alum-precipitated vaccine.

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### AGGLUTINATION TITERS

[illegible]

Per Cent Titers

2 wk.-3 mo.	189	89	173	130	294	287	763	377	52	39	2,393	7.90	3.72	7.23	5.43	12.29	11.99	31.89	15.75	2.17	1.63
3-6 mo.	122	52	87	248	261	411	472	324	111	87	2,175	5.61	2.39	4.00	11.40	12.00	18.90	21.70	14.90	5.10	4.00
6-12 mo.	65	41	39	107	145	106	314	198	53	13	1,081	6.01	3.80	3.61	9.90	13.41	9.80	29.05	18.32	4.90	1.20
12-18 mo.	57	75	131	53	44	141	219	131	35	22	908	6.28	8.26	14.43	5.84	4.84	15.53	24.12	14.43	3.85	2.42
18-24 mo.	42	22	35	33	66	60	156	296	39	17	786	5.28	2.76	4.60	4.14	8.29	7.54	19.60	37.18	8.67	2.14
2-3 yr.	20	9	62	67	51	173	181	120	29	15	757	2.75	1.24	8.53	9.21	7.01	23.80	24.90	16.51	3.99	2.06
3-5 yr.	22	7	111	57	83	53	45	178	30	24	610	3.61	1.14	18.20	9.34	13.61	8.69	7.38	29.18	4.92	3.93

### AGGLUTINATION TITERS

AGE GROUP*	TOTAL POSITIVE		SLIGHTLY POSITIVE (1:10 to 1:40)		STRONGLY POSITIVE (1:320 to 1:2,560)		MODERATELY POSITIVE (1:80 to 1:160)	
	NO.	%	NO.	%	NO.	%	NO.	%
2 wk. to 3 mo.	2,204	92.10	392	16.38	581	24.28	1,231	51.44
3 to 6 mo.	2,053	94.39	387	17.79	672	30.90	994	45.70
6 to 12 mo.	1,016	93.99	187	17.31	251	23.21	578	53.47
12 to 18 mo.	851	93.72	259	28.53	185	20.37	407	44.82
18 to 21 mo.	754	94.72	90	11.30	126	15.83	538	67.59
2 to 3 yr.	707	97.25	138	18.98	224	30.81	345	47.46
3 to 5 yr.	588	97.39	175	28.68	136	22.30	277	45.41

III. *Comparative Value of the Type of Pertussis Vaccine on Agglutinin Response of Young Infants.*—Fluid, alum-precipitated, and combined vaccines were administered to 5,028 Negro infants below the age of 3 months, according to the schedule in Table III.

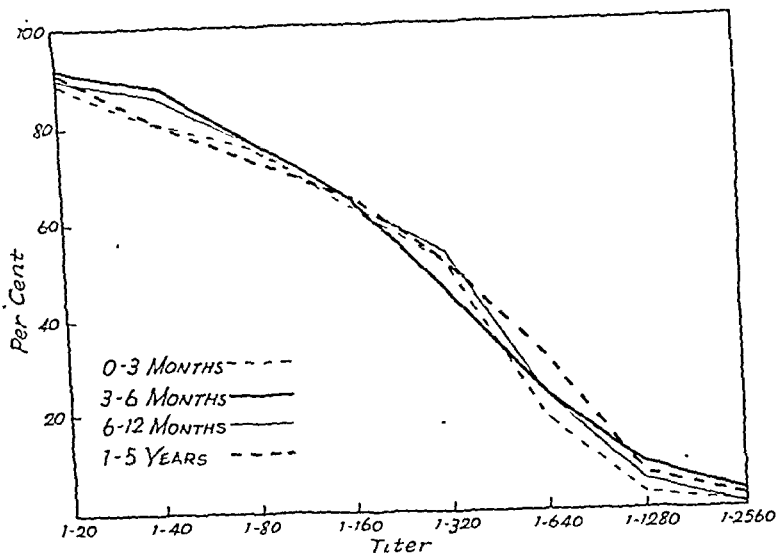


Fig. 1.—The effect of age on the agglutinin response to pertussis immunization with alum-precipitated vaccine.

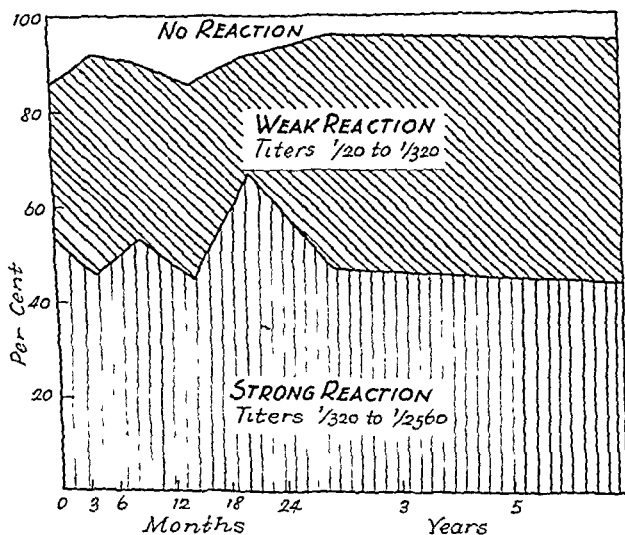


Fig. 2.—The effect of age on the degree of agglutinin response to pertussis immunization with alum-precipitated vaccine.

The results (Table IV) show conclusively that the fluid vaccines are definitely inferior in agglutinin production to alum-precipitated pertussis vaccine in the immunization of very young infants. The fluid vaccines (A and B)



TABLE III. SCHEDULE OF PERTUSSIS IMMUNIZATIONS WITH VARIOUS TYPES OF VACCINES

AGE	TYPE OF VACCINE AND DOSE				
	FLUID VACCINE		ALUM-PRECIPTATED VACCINE		PERTUSSIS VACCINE COMBINED WITH DIPHTHERIA AND TETANUS TOXOIDS (ANHYDROX)
	TYPE A (20 BILLION PER C.C.)	TYPE B (40 BILLION PER C.C.)	TYPE C (40 BILLION PER C.C.)	TYPE D (20 BILLION PER C.C.)	TYPE E (MIXED)
1-2 mo. (first dose)	1 c.c.	0.5 c.c.	0.2 c.c.	0.5 c.c.	1.0 c.c. vaccine D
2-3 mo. (second dose)	2 c.c.	1.0 c.c.	0.3 c.c.	1.0 c.c.	1.0 c.c. vaccine B
3-4 mo. (third dose)	2 c.c.	1.0 c.c.	0.5 c.c.	1.0 c.c.	1.0 c.c. vaccine D
Total dose	100 billion	100 billion	40 billion	50 billion	80 billion

TABLE IV. THE COMPARATIVE VALUE OF THE TYPE OF PERTUSSIS VACCINE IN THE AGGLUTININ RESPONSE OF YOUNG INFANTS

TABLE IV. THE COMPARATIVE VALUE OF ANTITOXIN AND ANTISEPTIC

TYPE OF VACCINE	AGGLUTINATION TITERS										Per Cent Titers												
	Number Titers										Per Cent Titers												
	0	1:10	1:20	1:40	1:80	1:160	1:320	1:640	1:1,280	1:2,560	TOTAL	0	1:10	1:20	1:40	1:80	1:160	1:320	1:640	1:1,280	1:2,560		
Fluid	A	91	43	91	172	109	70	88	32	19	7	722	12.60	4.96	12.60	42.38	24.80	15.10	12.19	4.43	2.63	0.97	
	B	138	43	165	218	144	146	134	104	31	16	1,139	12.12	3.78	14.49	37.41	25.46	12.64	12.82	11.76	9.13	2.72	1.40
Alum Precipitated	C	98	16	91	53	118	122	315	145	31	18	1,007	9.73	1.59	9.01	15.89	23.83	11.72	12.11	31.28	14.40	3.08	1.79
	D	148	86	207	127	173	197	169	125	40	22	1,294	11.44	6.65	16.0	32.46	28.39	13.37	15.22	3.06	9.66	3.09	1.70
Combined Vaccine	E	90	32	118	70	88	132	176	126	24	10	866	10.39	3.70	13.63	25.41	25.40	10.16	15.24	20.32	14.55	2.77	1.15
	F	90	32	118	70	88	132	176	126	24	10	866	10.39	3.70	13.63	25.41	25.40	10.16	15.24	20.32	14.55	2.77	1.15

gave 20.22 per cent and 25.01 per cent strong agglutinin titers (1:320 or above), whereas the alum-precipitated vaccine (C) gave 50.55 per cent. The pertussis vaccine combined with aluminum hydroxide-adsorbed diphtheria and tetanus toxoids (D) gave an intermediate value of 27.51 per cent, whereas, when one dose of fluid vaccine B was given between the two doses of vaccine D (type E), as recommended by Miller, strong agglutinin titers occurred in 38.79 per cent of the cases.

Sauer<sup>4</sup> has recommended immunization after the age of 7 months on the basis of his finding that only 27 per cent of eighty-nine infants developed strong complement fixing antibodies following immunization with *Hemophilus pertussis* vaccine given at or below the age of 3 months, whereas over 70 per cent of the infants inoculated at an older age showed strongly positive complement fixation tests. In Sauer's study, pertussis occurred seven times more frequently among children inoculated before the age of 3 months than among those inoculated after 7 months of age. A study of his data will indicate, however, that immunization of infants under 3 months of age was of value, since the attack rate in the immunized group was lower than in a similar non-immunized group, the disease in these infants was mild, and none died. Nevertheless, Sauer recommended the seventh month as the optimum age for pertussis immunization.

There have been objections to the agglutination test as a measure of antibacterial immunity. It serves as a convenient method for the determination of only one of many specific antibodies. Our studies show that the quantitative agglutinin titers generally correspond to quantitative complement fixation titers but not to qualitative complement fixation tests which are used by many investigators and which should be abandoned. "These methods of reporting results (1+, 2+, 3+, 4+) and the inference that the number represents a scale of positivity is, however, fundamentally and completely in error and should be abandoned. Classifications based on degree of lysis are devoid of quantitative significance" (Eagle<sup>5</sup>). Furthermore, subsequent studies reveal that the protective power of serum can be correlated quite closely to the agglutinin titers under challenge of exposure.

The data presented seem to indicate that the relatively poor response which Sauer obtained in the young infants may be attributed to the use of fluid vaccine. Perhaps in young infants prolonged antigenic stimulus by alum precipitation is required. In a recent publication,<sup>6</sup> Sauer states: "It has been firmly established that for infants less than six months of age only alum-precipitated pertussis vaccine should be used."

IV. *Evaluation of the Effect of Various Types of Pertussis Vaccine on the Incidence and Severity of Reactions in the Immunization of Young Infants.*—The incidence of local and systemic reactions to the fluid, alum-precipitated, and combined vaccines administered to young infants were analyzed as in our previous communication.<sup>1</sup> The local reactions were measured by the parents and were classified as mild, moderate, and severe, depending on whether their diameters were less than 2.5 cm., between 2.5 and 5 cm., or more than 5 cm. respectively. The fourth category included reactions in which abscess forma-

tion occurred. Small, deep, palpable nodules were not classed as a reaction. The systemic reactions were classed as mild, moderate, or severe depending on whether symptoms persisted less than twenty-four hours and/or were accompanied by a moderate fever or a high fever lasting more than two days, respectively.

A glance at Table V shows that local and systemic reactions occurred far less frequently with the alum precipitated vaccine than with the fluid vaccines and slightly less than with the combined vaccine (anhydrox), but abscesses occurred in 1.5 per cent with the alum vaccine, whereas the fluid and combined vaccine gave abscesses very rarely. Abscess formation with the alum-precipitated vaccine may be avoided by: (1) deep subcutaneous or intramuscular injection as recommended by Bell;<sup>7</sup> (2) avoiding intracutaneous inoculation as recommended by Sako and associates;<sup>4</sup> (3) directing the needle downward as recommended by Sauer.<sup>6</sup> Observations on older children, however, indicate that reactions occur much more frequently with the alum-precipitated vaccine. It was observed in the course of this study that in the immunization of older infants and children the combined vaccine is the product of choice since it gives far less reactions than the fluid product.

*V. Relationship of Local and Systemic Reactions to Agglutinin Titers.*—Local and systemic reactions are productive of agglutinins in higher titer than if no reactions occurred (Table VI). As a general rule, the more severe the reaction the higher the titer. Systemic reactions induced the production of higher agglutinin titers than local reactions. Abscess formation was associated with high agglutinin titers (1:1280 or above) in the fifty-five cases observed.

The mechanism by which reactions produce higher antibody titers is not known. Perhaps greater stimulus is placed on the reticuloendothelial system. Febrile infections often give rise to secondary nonspecific rise in antibodies (anamnestic reaction). Numerous studies show that intradermal inoculation is followed by the development of antibodies (Dick test, Schick test, intradermal typhoid immunization). Experiments designed to demonstrate the local formation of antibodies at the site of intradermal inoculation have yielded equivocal results. However, systemic production of antibodies may be efficiently carried out by the skin due to the richness of the dermis in reticuloendothelial cells.

*VI. Duration and Stability of Agglutinin Titers Following Pertussis Immunization of Young Infants With Alum-Precipitated Vaccine.*—Miller and co-workers,<sup>8</sup> Lapin,<sup>9</sup> Mishulow,<sup>10</sup> and others have found that in older infants and children pertussis agglutinins persist in the blood in relatively high titer for several years (two to six years). Miller and associates<sup>8</sup> observed no downward trend in antibody titer. Furthermore, the vast majority evidenced a relatively constant antibody level. A study of Table VII confirms the observation of the authors mentioned above. In young infants, the height of antibody titer is reached in from two to four months after completion of immunization, after which a plateau is maintained for three years or longer. Moreover, analysis of individual cases reveals that the agglutinin titer of any given infant remained fairly constant for the three-year period of observation.

TABLE V. INCIDENCE AND SEVERITY OF LOCAL AND SYSTEMIC REACTIONS IN YOUNG INFANTS FOLLOWING INOCULATIONS WITH FLUID, ALUM-  
PRECIPITATED, AND COMBINED PERTUSSIS VACCINES

	FLUID VACCINE				ALUM-PRECIPITATED VACCINE				PERTUSSIS VACCINE COMBINED WITH DIPHTHERIA AND TETANUS TOXOIDS (ANHYDROX)			
	TYPE A		TYPE B		TYPE C		TYPE D		TYPE E		NO.	%
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%		
Total inoculations	2,166		3,417		3,021		3,882		2,598			
<i>Local Reactions:</i>												
Mild	247	11.4	301	8.8	157	5.2	228	8.8	285	11.0		
Moderate	178	8.2	209	6.1	52	1.7	121	4.7	117	4.5		
Severe	78	3.6	76	2.2	5	0.14	39	1.5	71	2.7		
Abscess	4	0.2	2	0.06	44	1.5	0		1	.04		
Total	507	23.4	588	17.16	258	8.5	388	15.0	474	18.24		
<i>Systemic Reactions:</i>												
Mild	269	12.4	324	9.5	184	6.1	249	6.4	249	9.6		
Moderate	149	6.9	198	5.8	33	1.1	99	2.6	99	3.8		
Severe	50	2.3	62	1.8	7	0.22	47	1.3	49	1.9		
Total	468	21.6	584	17.1	224	7.4	397	10.3	397	15.3		

TABLE VI. RELATIONSHIP OF LOCAL AND SYSTEMIC REACTIONS TO AGGLUTININ TITERS

AGGLUTININ TITERS										
REACTIONS	TOTAL	1:10	1:20	1:40	1:80	1:160	1:320	1:640	1:1,280	1:2,560
<i>Local Reactions:</i>										
Mild	216	23 (10.8%)	16 (7.7%)	10 (4.9%)	26 (12.2%)	40 (18.6%)	62 (28.7%)	29 (13.7%)	6 (2.8%)	1 (1.7%)
Moderate and severe	137	10 (7.1%)	7 (5.4%)	7 (5.4%)	12 (8.5%)	17 (12.6%)	15 (32.7%)	24 (17.2%)	9 (6.7%)	6 (4.4%)
No reaction	265	31 (11.8%)	17 (6.5%)	17 (6.5%)	31 (11.6%)	34 (13.0%)	90 (33.8%)	34 (12.7%)	8 (2.9%)	3 (1.2%)
<i>Systemic Reactions:</i>										
Mild	234	25 (11.0%)	11 (4.7%)	14 (6.2%)	21 (9.2%)	24 (10.4%)	74 (31.7%)	41 (17.7%)	14 (5.9%)	10 (4.3%)
Moderate and severe	168	15 (9.1%)	5 (3.0%)	6 (3.6%)	9 (5.4%)	14 (8.4%)	36 (21.2%)	45 (26.5%)	23 (13.9%)	15 (8.8%)
No reaction	265	31 (11.8%)	17 (6.5%)	17 (6.5%)	31 (11.6%)	34 (13.0%)	90 (33.8%)	34 (12.7%)	8 (2.9%)	3 (1.2%)

TABLE VII. DURATION AND STABILITY OF AGGLUTININ TITERS FOLLOWING PERTUSSIS IMMUNIZATION WITH ALUM-PRECIPTATED VACCINE IN 786 YOUNG INFANTS

TITER	AFTER COMPLETION OF IMMUNIZATION					
	2 TO 6 MO.	6 TO 12 MO.	12 TO 18 MO.	18 TO 24 MO.	24 TO 30 MO.	30 TO 36 MO.
1:2,560	13	15	17	12	16	15
1:1,280	24	23	25	33	29	28
1:640	123	122	131	150	171	148
1:320	259	265	261	236	215	235
1:160	99	92	97	91	95	86
1:80	99	104	98	104	104	108
1:40	37	42	40	32	31	38
1:20	51	47	44	48	60	59
1:10	30	23	25	35	21	29
0	51	53	48	45	44	40

VII. *Effect of "Stimulating Dose" of Pertussis Vaccine on the Agglutinin Titers of Infants Immunized Below the Age of 3 Months.*—Young infants below the age of 3 months were immunized with the alum-precipitated pertussis vaccine (40 billion per cubic centimeter) as previously described. The agglutinin titers were determined two to four months following completion of immunization and again just before 0.5 c.c. of the "stimulating dose" which was approximately eight to twelve months after the last inoculation. It can be readily seen (Table VIII) that within one month after revaccination the agglutinin titers rose markedly in the vast majority of cases. It is interesting that some children with negative titers were never able to develop any antibodies in spite of repeated "stimulating" inoculations. All cases exposed to pertussis were excluded from this study.

TABLE VIII. EFFECT OF "STIMULATING DOSE" OF 0.5 C.C. ALUM-PRECIPTATED PERTUSSIS VACCINE ON THE AGGLUTININ TITERS OF 368 INFANTS IMMUNIZED BELOW THE AGE OF 6 MONTHS

TITER	BEFORE "STIMULATING DOSE"	AFTER "STIMULATING DOSE"				
		1 MO.	6 MO.	12 MO.	18 MO.	24 MO.
1:2,560	6	56	58	56	58	65
1:1,280	11	183	123	139	130	132
1:640	65	85	59	55	56	66
1:320	114	54	45	44	51	42
1:160	47	27	24	23	22	15
1:80	45	15	16	15	11	12
1:40	20	8	7	9	12	10
1:20	24	14	12	14	14	16
1:10	15	9	8	6	7	5
0	21	7	6	7	7	6

VIII. *Incidence and Severity of Pertussis Upon Exposure in Immunized and Nonimmunized Children with Known Agglutinin Titers.*—Out of over 40,000 young infants below 3 months of age who were immunized with pertussis vaccines, 493 whose agglutinin titers were known and followed periodically every three to six months were exposed to pertussis within the household. As controls, 438 young nonimmunized infants of comparable age, whose agglutinin titers were negative and who were similarly followed periodically, were exposed to pertussis. The diagnosis of pertussis was made clinically by the author after

thorough examination and repeated observations. Table IX shows conclusively that the incidence and severity of pertussis was far greater among the nonimmunized (89.7 per cent) than in the immunized (13.2 per cent). It is very significant that pertussis did not occur in the immunized children with agglutinin titers of 1:320 or above in spite of prolonged exposure, the exposed child often sleeping in the same bed with an older child having the disease. On the other hand, many exposed children with low or negative agglutinin titers also escaped the disease. This supports Miller's observation<sup>11</sup> that, although immunity may exist in the absence of agglutinins, susceptibility is not present in the presence of agglutinins in high titer (1:320 or above).

TABLE IX. INCIDENCE AND SEVERITY OF PERTUSSIS UPON INTIMATE FAMILIAL EXPOSURES IN IMMUNIZED AND NONIMMUNIZED CHILDREN WITH KNOWN AGGLUTININ TITERS

TITER	TOTAL	CASES	PER CENT	SEVERITY			ESCAPES	
				MILD	MOD.	SEVERE	NO.	%
Immunized*								
1:2,560	12	0	0.0				0	100.0
1:1,280	27	0	0.0				0	100.0
1:640	48	0	0.0				0	100.0
1:320	62	0	0.0				0	100.0
1:160	53	6	11.3	6	0	0	47	88.7
1:80	75	8	10.7	7	2	0	67	89.3
1:40	91	17	18.7	12	4	0	74	81.3
1:20	82	21	25.6	18	2	1	61	75.4
1:10	16	4	25.0	2	1	1	12	75.0
0	27	9	33.3	4	3	2	18	66.7
Total	493	65	13.2	49	12	4	279	86.8
Nonimmunized controls†								
Titer negative	438	393	89.7	43	291	59	45	10.2

\*No deaths.

†Three deaths.

#### SUMMARY

Contrary to popular opinion, young infants are able to produce antibodies as a result of pertussis immunization just as well as older children. In the immunization of these young infants, prolonged antigenic stimulus as afforded by alum precipitation is necessary for efficient antibody production. The alum-precipitated vaccine, except for its tendency to produce sterile abscesses, gave far less local and systemic reactions than the fluid or combined vaccines. Severe reactions were an infrequent occurrence with the young infants. Local and systemic reactions were associated with high agglutinin titers indicating that, although undesirable from the practical standpoint, they are highly desirable immunologically.

Following pertussis immunization the agglutinins reach a plateau level in two to four months and remain at this level practically unchanged for at least three years. A "stimulating dose" of pertussis vaccine administered eight to twelve months following completion of immunization of young infants raises the agglutinin titer to higher levels within one month, after which the plateau is maintained for two years or longer.



A follow-up of immunized and nonimmunized children with known agglutinin titers shows that immunization of young infants below 3 months of age is highly effective and supports the contention that, although immunity may exist in the absence of agglutinins, susceptibility does not occur in the presence of agglutinins in high titers (1:320 or above).

#### RECOMMENDATION

Data have been presented to show that immunization of young infants below 3 months of age is immunologically sound and highly effective if an alum-precipitated vaccine is used. On the basis of these findings, physicians are urged to institute a program of early immunization against pertussis on a nationwide basis.

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# THE TREATMENT OF ALLERGIC PATIENTS WITH BENADRYL

## A REPORT OF SEVENTY-NINE CASES

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THE problem of effecting a practical and suitable therapeutic antihistamine agent with comparatively safe and little toxic properties occupied the minds of investigators for many years. Atropine was used, but the dosage had to be too great to be of any clinical use. Dale and Richards,<sup>1</sup> in 1918, used epinephrine, which proved too potent and fleeting to be practical. Bovet and Staub<sup>2</sup> of France, in 1937, made a systematic search among the Fournieu series of chemicals for a practical antihistamine compound and developed two potent antihistamine substances known as 1571 F and 929 F. However, the disagreeable and toxemic responses to these drugs made their clinical usefulness impossible. Mayer and associates,<sup>3</sup> in 1945, synthesized a similar but less toxic antihistaminic chemical compound known as  $\alpha$ -pyridinoethylenediamine. About the same time, in the research laboratories of Parke, Davis & Co., Rieveschl and Huber synthesized the antihistaminic chemical compound known as Benadryl (B-dimethylaminoethyl benzyhydril ether hydrochloride). Loew and his associates,<sup>4</sup> working in the same laboratories, tested the toxicity of benadryl in rats and guinea pigs, and found it to be very low. They also made pharmacologic studies of its effects upon animals. In an untreated control group of guinea pigs with induced histamine shock they obtained 100 per cent mortality rate. When adequate doses of aminophyllin were offered to a group of animals with histamine shock, the mortality was 47 per cent, and when such guinea pigs received benadryl the mortality rate was zero. Loew noted immediate relief of the bronchial spasm and vasomotor depression in the benadryl treated animals. Hallenbeck and associates<sup>5</sup> studied the antispasmodic effect of benadryl upon histamine treated, ileum muscle strips, in vitro, and found it 650 times as effective as papaverine in antispasmodic effect. Curtis and Owens,<sup>6</sup> in 1945, administered benadryl to eighteen allergic patients, reporting therapeutic effectiveness and low toxicity. McElin and Horton<sup>7</sup> observed a patient known to have hypersensitiveness to cold. The blood histamine of this patient had risen during and immediately after a period of active response to cold, demonstrating that "H" substance in this case was definitely histamine. They produced a typical wheal and flare on the patient's forearm by holding a standard sized ice cube on one spot for three minutes. Then benadryl was given intravenously for ten minutes and the cube of ice was applied to the opposite forearm for a similar period. Response to the ice cube on this occasion was estimated to be about 50 per cent less than that produced before the giving of benadryl. This may be one of the most definitive demonstrations of histamine antagonism. The symposium on benadryl as an antihistamine substance and its use in urticaria, bronchial asthma, and hay fever, and allergic diseases of childhood<sup>8</sup> confirm the findings of Curtis and Owens<sup>6</sup> and of Loew and associates.<sup>9</sup>

## PLAN OF STUDY

In a recent clinical study from January, 1946, to July, 1946, the value of benadryl was tested by administering it to seventy-nine patients with allergy. The results are tabulated in Table I. In Tables II and III the dosage and duration of treatment and the secondary effects of benadryl are recorded.

TABLE I. RESULTS IN SEVENTY-NINE PATIENTS WITH ALLERGIC CONDITIONS

DIAGNOSIS	CASES (NO.)	AGE (YR.)	SEX		RESULTS			
			M	F	EXCELLENT	GOOD	FAIR	NOT IMPROVED
Recurrent, chronic urticaria	8	3-6	5	3	8	0	0	0
Urticaria with angioneurotic edema	3	2-5	1	2	3	0	0	0
Hay fever, spring and early summer, seasonal	23	4-11	10	13	19	3	1	0
Hay fever and asthma	6	9-12	3	3	4	1	1	0
Asthma	9	10-35	6	3	6	0	1	2
Vasomotor rhinitis	13	6-16	7	6	13	0	0	0
Polypoid ethmoiditis with alternate nasal clogging and drip with forced mouth breathing, rhinorrhea, and dyspnea	2	16 and 30	2	0	1	1	0	0
Acute urticaria, food allergy of fish, berry, and spinach	4	6-10	2	2	4	0	0	0
Migraine type cephalgia	3	13-20	1	2	0	1	1	1
Ménière's disease	4	16-30	0	4	0	1	1	2
Contact dermatitis with eczematous lesions	4	6-16	3	1	1	2	0	1

TABLE II. DOSAGE AND DURATION OF BENADRYL TREATMENT IN SEVENTY-NINE CASES

AGE (YR.)	CASES (NO.)	DAILY DOSE (MG.)		DURATION OF TREATMENT	REMARKS
		MINIMUM	MAXIMUM		
2	2	20	50	One month	For attacks and continuance; administered elixir benadryl, each teaspoon equals 10 mg.
3 to 6	34	30	50	One week to two months	Benadryl Kapseals, each 50 mg.; elixir given to young child
6 to 13	30	100	150	Two weeks to two months	Three children received the maximum dose for two days, then the minimum dose; others, minimum
13 to 16	5	100	150	One month to three months	One child received maximum dose for three days and felt too sleepy; dose reduced to minimum
Above 16	8	100	200	Two weeks to five months	Two cases tolerated maximum dose; three received 150 mg.

TABLE III. SECONDARY EFFECTS; ANALYSIS OF SEVENTY-NINE CASES

SECONDARY EFFECTS	CASES	REMARKS
Drowsiness	45	Very mild in most patients
with vertigo	6	The symptoms were mild to moderate.
with diplopia	2	25 mg. pyridoxine given with benadryl
with dry mouth	26	diminished or cleared up the secondary
with fatigue	3	effects and drowsiness; in two cases,
without other symptoms	8	50 mg. niacinamide daily was necessary
Jittery feeling	16	Reduced the maximum dose to the daily
Mild nausea and bad taste in mouth	3	minimum dosage; symptoms cleared up
No side effects	15	Pyridoxine, 25 mg. daily, gave relief

Benadryl was given during attacks of urticaria whether it was an acute condition, a recurrent or chronic attack. The response was noticeable in one-half to one hour after administration and lasted about twelve hours. Similar favorable responses were observed in children with hay fever, those who suffered from asthma, and the sufferers from hay fever and asthma combined. In three adult asthma patients, one showed a fair response and two showed no improvement. The vasomotor rhinitis and polypoid ethmoiditis individuals responded miraculously to the benadryl therapy. The contact dermatitis patients with or without eczema gave moderately fair results, while the migraine type of cephalgia and the patients with Ménière's disease responded from fair to poor. All were treated for the attacks and given the maximum daily dose of benadryl as shown in Table II. If relief was obtained, continuous treatment with minimum dosage of benadryl was given daily for periods varying from one week to two months, depending upon the condition and the individual patient. This regimen of treatment, continuing the administration of benadryl, allows the child to eat the allergic foods or live in a pollen saturated area, and at the same time be kept free from symptoms. One child suffered from severe hives when eating spinach. While taking benadryl, she was able to eat a saucerful of spinach and yet be free from any wheals or flare-ups. Several children were attacked with severe asthma wheezing and dyspnea in the presence of fish in the home. While taking benadryl, the same children were able to eat fish and be entirely free from asthma attacks. The treatment with benadryl was kept up from four to eight weeks, after which most children remained free from recurrent attacks of their allergic disease. In a few instances where children had a relapse of allergic symptoms of their condition they received another course of treatment with benadryl for one or two months. In every case benadryl was administered beginning with the minimum dose for the age of the patient, and if there was no therapeutic response in from one-half to one hour the dose would be considered inadequate and hence increased.

#### DISCUSSION

Benadryl appears to belong to a pharmacologic group which has the property of preventing some of the pharmacologic effects of histamine. Histamine seems to be held as such within the cells and released rapidly when they are damaged. The release of histamine or histamine-like substances has been held responsible in whole, or in part, for the presenting complaint in the majority of cases reported in Table I. Benadryl seems to diminish the amount of histamine to be released in the cells, thereby relieving the symptoms of the allergic patients. Benadryl may also act at the source of change of histadine to histamine through the carboxylase bacteria. Our present knowledge of the pharmacologic action of benadryl and our observations of its therapeutic action clinically in allergic patients, leads us to conclude that it offers symptomatic relief in urticaria, vasomotor rhinitis and ethmoiditis, in hay fever and asthma of children, and other allergic manifestations.

## SUMMARY

The clinical findings in seventy-nine allergic patients treated with benadryl, of whom seventy-one are children and eight adults, are reported. The ages of the children are from 2 to 16 years, and the adults from 19 to 35 years, with their sex about equally distributed. The favorable responses to benadryl administration show 76 per cent of all groups have excellent improvement, 10 per cent good, 6 per cent fair to poor, and 8 per cent no improvement. It is interesting to note that when pyridoxine hydrochloride 25 mg., was added to each dose of benadryl, the drowsy feeling wore off. This was found particularly useful for students especially when they had to attend lecture courses. It also diminished nausea, vertigo and diplopia, these occurring but rarely. In two patients on whom pyridoxine hydrochloride did not remove the secondary effects, 50 mg. niacinamide were given, and the side effects of vertigo and nausea were immediately relieved. In general, the side effects or toxicity from benadryl were very mild, while its therapeutic effects were potent and beneficial. Benadryl can be administered safely and effectively. It should be used with caution and only where indicated.

I wish to thank Mr. Ranaghan, Mr. Murray, and Mr. Cundiff from the Parke, Davis & Co. research laboratories for supplying the Benadryl Kapseals and Elixir to carry on this clinical research study.

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## TREATMENT OF ACUTE DIARRHEA IN THE CINCINNATI GENERAL HOSPITAL DURING THE YEARS 1944 AND 1945

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**D**IARRHEA and enteritis, considered as an entity, ranks second in the causes of death in infancy and childhood.<sup>1</sup> It occupies, by virtue of its high morbidity, a large part of many pediatric services in this and other countries. Annually, in the five years from 1935 to 1940 over 10,000 children in the United States under 2 years of age died of diarrhea. In Cincinnati between 1939 and 1941 there were three times as many deaths from diarrhea as from diphtheria, scarlet fever, and pertussis combined.<sup>2</sup> Despite local efforts to prevent and treat the disease, Cincinnati's resident death rate from diarrhea compared with cities of comparable size is among the highest in the country. The white death rate is 50 per cent above the average, the Negro rate 12.5 per cent below the average of thirteen cities (1939 through 1941).

Compared with similar data compiled from 1929 through 1931, there has been some improvement. During the earlier period Cincinnati had the highest white death rate, while it now has the fourth highest. The Negro death rate in 1929 through 1931 was also highest; now it is sixth highest.

In Cincinnati we therefore have had an opportunity to study large numbers of cases of severe, neglected diarrhea each year, and have tried many types and plans of therapy. In the past two years at the Cincinnati General Hospital we have employed continuous intravenous therapy with great success in the treatment of all children acutely ill with diarrhea. The methods and techniques employed have evolved gradually over the two-year period as a result of clinical experience both at Cincinnati Children's Hospital and Cincinnati General Hospital. No single new procedure of therapy has been devised; what is new to a certain extent is the emphasis on consistent, planned, continuous, intravenous therapy, the duration and character of which is determined by the clinical course of the disease and the derangement of the fluid balance of the patient.

*I. Plan of Therapy.*—On admission, the patient is taken at once to the treatment room. Blood is drawn for determination of the carbon-dioxide combining power and serum chloride. A stool culture is obtained at this time. A needle is inserted into the patient's wrist or foot for continuous intravenous fluid administration. The fluid therapy is begun with normal saline. About 10 c.c. per pound of body weight is given by injection over a period of several minutes, and then the continuous intravenous drip is started either with saline or 5 per cent glucose in saline, the drip being regulated to provide at an even rate the estimated fluid required over the next twenty-four hours. The fluid requirement in the first twenty-four hours following admission is calculated from

From the Children's Hospital Research Foundation and the Pediatric Department of the University of Cincinnati School of Medicine.

simple empirical rules. If the patient is moderately dehydrated, he receives his usual saline requirements of 100 to 125 c.c. for infants,<sup>3</sup> plus an additional 5 per cent of his body weight as saline-containing fluid; physiological saline, glucose in saline, plasma, blood, or any combination of these fluids. If severely dehydrated, he receives the daily saline requirements plus 10 per cent of his body weight as saline-containing fluids. Within an hour after admission, the blood carbon-dioxide combining power has been reported. If it is less than 30 volumes per cent, it is corrected to 40 to 45 volumes per cent by the injection of 3.75 per cent sodium bicarbonate solution, following which the continuous drip is resumed; if the carbon-dioxide combining power is greater than 30 volumes per cent, no correction is usually made.

TABLE I. DIARRHEA AND ENTERITIS IN THIRTEEN CITIES OF THE UNITED STATES

RESIDENT DEATH RATES (PER 100,000 POPULATION) OF INFANTS UNDER 2 YEARS OF AGE*			
WHITE RACE		NEGRO RACE	
CITY	DEATH RATE	CITY	DEATH RATE
Cleveland	64	Kansas City	36
St. Louis	75	Cleveland	114
Memphis	79	Memphis	165
Kansas City	86	Birmingham	243
Birmingham	109	Pittsburgh	265
Atlanta	156	Indianapolis	290
New Orleans	159	St. Louis	304
Indianapolis	172	Cincinnati	378
Pittsburgh	189	New Orleans	406
Cincinnati	247	Columbus	482
Baltimore	250	Atlanta	499
Columbus	272	Washington	748
Washington	300	Baltimore	840
Average of thirteen cities		164	Average of thirteen cities 433

\*Average of 3 years (1939 through 1941).

Thereafter, in each twenty-four-hour period the patient is given enough saline-containing fluid to satisfy his daily requirement (100-125 c.c.) and, if diarrhea continues, to replace electrolyte lost in the stools. The remainder of the daily fluid intake (based on a minimum daily requirement of 120 c.c. per kilogram or  $2\frac{1}{4}$  ounces per pound) is given as 5 per cent glucose in water. Plasma is given on admission instead of normal saline solution if the patient is in shock or severely malnourished. Whole blood transfusions are frequently employed after hydration is accomplished, as the hemoglobin concentration often falls to values of 7 to 9 Gm. per cent following restoration of circulating blood volume.

Each patient's "intravenous progress" is followed on two sheets: one sheet is kept by the nurses to indicate the type and amount of fluid administered, and one is kept by the house staff to summarize the intake of calories, protein, saline-containing fluids, and total fluid volume for each twenty-four-hour period.

Often the diarrhea subsides completely within twenty-four to thirty-six hours, and at this point small amounts of 5 per cent glucose in water or saline ( $\frac{1}{2}$  to 1 ounce) are given by mouth every three hours. If the initial two feedings of clear fluid are retained, formula, either boiled, skimmed milk or skimmed

milk plus 10 per cent corn syrup, is fed in small amounts (about 1 ounce) every three hours. The intravenous infusion by that time is usually discontinued. Skimmed milk is then given every three hours for twenty-four hours, and, if there is no recurrence of the diarrhea, is increased gradually in amount until the patient is receiving his daily fluid requirement by mouth. Until this time hypodermoclyses are given once or twice a day to supply as much extra fluid as is necessary to make up the total fluid requirement. Usually, after two to four days, the patient can be changed to an evaporated milk formula, and discharged within one to three days thereafter.

Sulfadiazine or sulfathiazole is given routinely to all patients shortly after admission, and continued until at least one negative stool culture is received from the laboratory. The drug is given subcutaneously every twelve hours while oral feedings are withheld, and thereafter is given orally every four hours in doses of grains 1 to  $1\frac{1}{2}$  per pound of body weight. Clinically, the course of the disease has not seemed to be affected by the administration of sulfonamides. There were only twenty-six patients in the two years (1944 through 1945) with proved dysentery, and it is in these patients alone that sulfonamide therapy is of benefit. A previous series of cases of diarrhea reported in 1941 by Cooper and others<sup>4</sup> failed to disclose a statistically demonstrable effect of sulfathiazole in the treatment of patients whose stools were negative for the dysentery organism.

For cases of chronic diarrhea the therapy is modified so that in addition to satisfying the daily needs for fluid and saline, as in the acute cases, the caloric and protein requirements are also met. To do this, a venesection is usually necessary, because of the hypertonic solutions used. Ten per cent glucose in water, 5 per cent casein hydrolysate solution in 10 per cent glucose, 5 per cent glucose in normal saline, plasma with 50 per cent glucose added (to make the equivalent of 10 per cent glucose in plasma) are used to provide at least 40 calories per pound and 1 to 2 Gm. of protein or amino acids per pound.

Following is the case report of a patient admitted during the summer of 1945 which may serve to illustrate the type of therapy employed.

#### CASE REPORT

W. M., a 6-week-old, white, male infant was admitted Aug. 20, 1945, with a history of diarrhea for two days, and vomiting for one day. He had been on a formula of evaporated milk since birth, and had had a previous bout of gastroenteritis. Physical examination on admission showed the infant to be very thin and malnourished, weighing 7 pounds, 1 ounce. Dehydration was marked, and the patient appeared acidotic.

*Laboratory Studies.*—Carbon-dioxide combining power, 24 volumes per cent; hemoglobin, 12.5 Gm. per cent; white blood cell count, 11,300; stool culture negative; urine negative.

*Course.*—A continuous intravenous infusion was started at 12 noon on Aug. 20, 1945, with 40 c.c. of 3.75 per cent sodium bicarbonate solution, followed by 275 c.c. of normal saline, and then 100 c.c. of 5 per cent glucose in saline and 120 c.c. of plasma, in addition to 500 c.c. of 5 per cent glucose in water. The diarrheal stools continued. On Aug. 22, 1945, the diarrhea ceased completely; the intravenous infusion was discontinued, for technical reasons, and the patient given an additional subcutaneous infusion later in the day. On Aug. 23, 1945, hypodermoclyses were again given, and the patient was started on 1 ounce of glucose water orally every two hours. After the patient had retained four of these feedings, skimmed milk was



started, in 1 ounce amounts. On Aug. 24, 1945, the skimmed milk was increased to 2 ounces every three hours; one hypodermoclysis of 5 per cent glucose in saline was given (200 c.c.); on that day the patient had three semisolid stools. On Aug. 25, 1945, the stools were normal and the skimmed milk was increased to 3 ounces every three hours; and on Aug. 26, 1945, the patient was placed on a standard evaporated milk formula, 4 ounces every four hours.

Sulfadiazine every twelve hours was given subcutaneously until Aug. 23, 1945 (grains  $3\frac{1}{2}$ ); thereafter, it was given orally, grains  $1\frac{1}{2}$  every four hours.

Clinically, the patient responded rapidly to the intravenous fluids, with prompt disappearance of the lethargy and irritability noted on admission; he took his feedings eagerly, as do most of the patients after a period of oral starvation. He was discharged on his eighth hospital day weighing 8 pounds 14 ounces.

II. *Complications of Therapy.*—Superficial areas of necrosis were noted several times in debilitated patients, at points where the arm or leg splints were inadequately padded; these healed with little or no scarring. One patient developed wrist drop from extreme flexion of the wrist; this cleared over a period of several months. There were three recorded cases of localized abscesses, all of which healed following incision and drainage. Thrombophlebitis and cellulitis about the site of the needle was often seen, but healed after treatment with massive wet saline compresses and sulfonamides. The only serious and permanent indictment of the therapy was the case of an infant who developed a cutaneous slough of the right wrist and gangrene of the left leg following continuous intravenous infusions containing calcium chloride; a supracondylar amputation was required for the left leg; the arm healed, but scarred with a moderate extension contracture.

III. *Results.*—In this series are included all of the patients with acute diarrhea or dysentery admitted to the pediatric ward of the Cincinnati General Hospital during 1944 and 1945, a total of 292 cases. Only patients with a discharge diagnosis of diarrhea, enteritis or bacillary dysentery are included; no patients with an additional diagnosis of any acute or chronic parenteral infection were studied. No cases were excluded except those which developed in premature infants, who are cared for in a separate nursery. The therapy was in all instances carried out by interns under the direction of a pediatric resident. The patients were all seen initially in the admitting room by the pediatric resident, at whose discretion they were admitted to the ward. Of all the patients with diarrhea in the outpatient department, only the most seriously ill were admitted, both because of shortage of beds and nursing help, and a reluctance to overburden the interns with mild cases that could be treated on an outpatient basis. Criteria for admission usually were: (1) marked dehydration and fever; (2) clinical acidosis; (3) persistent vomiting; and (4) failure of simple outpatient treatment measures. In 1944, 34 of 160 patients with diarrhea at the Cincinnati General Hospital received no parenteral fluids; in 1945 only 4 of 132 failed to receive parenteral fluids, an indication not of the increasing incidence of dehydrated patients so much as of an increased awareness on the part of the resident staff that even mildly dehydrated patients should have their fluid and electrolyte volume restored and that infants on insufficient oral feed-

ings to supply minimum needs of fluid require parenteral supplementation until adequate oral feedings are resumed. We think that it may be said that we deal with as severe cases of diarrhea as can be found reported anywhere in the literature.

Of the 292 patients with diarrhea included in this study, 223 were white, 69, Negro. There was a total of 22 deaths, 21 of these occurred in the white infants, one in a Negro infant. In 1944, 12 of 160 patients died, a fatality rate of 7.5 per cent; in 1945, 10 of 132 patients died, a fatality rate of 7.6 per cent. The combined fatality rate for the two-year period was 7.5 per cent, a 9.4 per cent fatality rate for the white race, and 1.5 per cent for the Negro.

Breaking this down into age groups gives a clear idea of the distribution of the disease in our series.

TABLE II. AGE DISTRIBUTION OF MORTALITY FROM DIARRHEA

AGE (MONTHS)	CASES	DEATHS*	FATALITY RATE (%)
0-3	87	11	12.6
4-6	66	6	9.1
7-12	68	3	4.4
13-18	27	1	3.7
19-36	20	0	0.0
37 up	24	1	4.2

\*It may be seen from this table that in 221 infants under one year of age twenty deaths occurred, a fatality rate of 9.1 per cent.

In an attempt to classify the severity of the disease in each patient, each case was placed in one of four categories: (1) *Mild*—diarrhea ceasing soon after admission and requiring little or no therapy; (2) *Moderate*—the variety of summer diarrhea that makes up the bulk of the admissions, with carbon-dioxide combining powers of 30 to 40 volumes per cent, fever, and moderate dehydration; (3) *Severe*—carbon-dioxide combining powers of 25 to 30 volumes per cent, fever, and marked dehydration; (4) *Very severe*—carbon-dioxide combining power less than 25 volumes per cent; extreme dehydration; high fever; patients often in shock or in extremis on admission.

TABLE III. SEVERITY AND MORTALITY OF DIARRHEA CLASSIFIED ACCORDING TO AGE

AGE (MONTHS)	MILD	NUMBER OF CASES		
		MODERATE	SEVERE	VERY SEVERE
0-3	3	37	26(1)*	21(10)
4-6	2	37	17	10(6)
7-12	5	42	16	5(3)
13-18	2	17	7	7(1)
19-36	3	12	4	1
37 up	4	17	2	1(1)
Total	19	162	72(1)	45(21)

\*Figures in parentheses indicate deaths.

In many instances, critically ill patients had high carbon-dioxide combining powers on admission, and we feel that the carbon-dioxide combining power cannot be considered a reliable guide to the severity of illness, but only to the severity of the concomitant acidosis. Nevertheless, we have kept the carbon-

dioxide combining power as a criterion of the seriousness of the disease, as it is one of the few objective measurements available. Carbon-dioxide combining powers under 40 volumes per cent were reported on the charts of 145 patients; 21 additional carbon-dioxide combining powers were reported from 41 to 50 volumes per cent; 126 patients had no blood carbon-dioxide combining power reported, the great bulk of these being in the first half of 1944, during which time our present plan of therapy was being crystallized.

It is difficult to resist the temptation to exclude certain cases and arrive at a "corrected mortality rate." There were twenty-two deaths in our series; of these, three occurred in patients who died within three hours of admission, before adequate therapy had been instituted. Another three were patients who died of other causes after their diarrhea had subsided: one had multiple congenital heart defects at autopsy and was marantic on admission, weighing 6 pounds at the age of 4 months, another died of a spontaneous pneumothorax on the eighth hospital day, and the third died on the sixteenth hospital day, following an episode of vomiting several days after all diarrhea had ceased. If one excludes these cases in which either the diarrhea was not the obvious cause of death or in which therapy could not be instituted before death, one arrives at a "corrected case fatality rate" of 5.6 per cent (sixteen deaths in 286 cases).

#### ETIOLOGY

1. *Feedings*.—The clinical impression that breast-fed babies do not contract diarrhea, or, if they do, contract a mild form of the disease that does not necessitate hospitalization or interruption of breast feedings, is amply supported by the fact that of the 221 infants in this series, only three were being breast-fed at the time of admission; one of these patients had such a mild diarrhea that he probably should not have been admitted, one had a chronic low-grade diarrhea, and only one had an acute diarrhea that had to be treated with continuous intravenous therapy.

2. *Specific Etiology*.—In 1944, in 140 of the 160 cases, one or more stool cultures were reported; 26, or 18.5 per cent, of these were positive for dysentery bacilli. In 1945, in 100 of 132 cases, stool cultures were reported; 8, or 12 per cent, of these contained dysentery bacilli. Two cultures revealed *Salmonella paratyphi B*. A number of the stool cultures were positive for *Shigella dispar*, the pathogenicity of which is open to question.<sup>5</sup> Disregarding the disputable virulence of these latter organisms, there were positive cultures for dysentery in 34 of 240 cases. Extrapolating, one can predict that 41 positive cultures would have been obtained had there been stool cultures in all 292 cases. There was one death from bacillary dysentery. Both patients with paratyphoid infection recovered; of the 249 patients with nonspecific diarrhea, 21 died. In other words, excluding all actual and predicted cases of specific diarrhea, the over-all death rate for all cases of acute nonspecific diarrhea is 8.5 per cent. This is one per cent higher than the death rate for the entire series, and may indicate that with the advent of sulfonamide therapy dysentery has become a less fatal disease in infancy than nonspecific diarrhea. Although at one time

parenteral infection was thought to be a common cause of severe diarrhea and vomiting in infancy, and is still so considered both in Great Britain and France, the diarrhea which occurred in infants at the Cincinnati General Hospital suffering primarily from parenteral infection was almost always so mild in nature as to affect little the prognosis of the basic disease and to require little additional therapy. As was stated earlier, all cases in which diarrhea was apparently secondary to parenteral infection were excluded from our series.

3. *Epidemiology*.—One is continually impressed by the part that poverty, ignorance, and substandard living conditions play in the production of diarrhea in infancy. Inability to comprehend feeding instructions, lack of money to comply with them even when the understanding is present, and inadequate housing, sanitary, and cooling facilities, are all factors that impress one after even a brief experience with the parents of these children. With the high incidence of diarrhea in Cincinnati and the infrequency of diarrheas in the more northern metropolitan areas one might think that climate would be a decisive factor; yet Memphis, Birmingham, Atlanta, and New Orleans all had lower white mortality rates than Cincinnati, and, of these more southerly cities, all but Atlanta had lower Negro rates,<sup>2</sup> suggesting that latitude is only a minor factor in the epidemiology of this disease. The majority of cases of diarrhea in Cincinnati come from an area which is inhabited by the poorest of the population, yet in the midst of the greatest concentration of diarrhea in this area there is an oasis, the government housing projects with adequate sanitation, refrigeration, and screening, from which only five of the 292 cases were admitted, while numerous cases dot the map in areas immediately adjacent to and surrounding these homes.

#### COMPARISON WITH OTHER SERIES

It is instructive to compare our series of cases with those reported elsewhere, difficult as it is to evaluate the severity of cases of diarrhea from different communities and in different years. In 1922 Monrad<sup>5</sup> reported from Stockholm the results of therapy with a "protracted water-diet": patients were starved from three to twelve days, and given water only by mouth and subcutaneous saline as needed. There were 50 deaths in 291 patients; of these, 131 had mild diarrhea, of whom 6 died and 21 developed chronic diarrhea; 160 of the patients were apparently sick enough to be compared with ours, and of these 44 died, and 29 developed chronic diarrheas, a mortality rate of 27.5 per cent. Four years later (1926) Powers<sup>6</sup> reported from New Haven in one of the first papers on planned therapy in infants with severe diarrhea, or, as he called it, "intestinal intoxication." He used subcutaneous and intraperitoneal fluids to combat dehydration, and gave liberal transfusions of whole blood. Food was withheld until toxic symptoms had greatly diminished; thereafter it was given in small, slowly increasing amounts. In 36 patients treated with planned therapy, only 12 died (33 per cent); of 19 not given this treatment, 14 (70 per cent) died. He omits from his series 9 patients who died within twelve hours of admission or were taken home against advice. In 1931 Karelitz and Schick<sup>7</sup> published the first paper on continuous intravenous treatment of diarrhea, an outgrowth

of observations that patients with surgical shock respond well to intravenous glucose solutions and that severe diarrhea is in many respects similar to surgical shock. When the patients with diarrhea were given intravenous infusions they responded well but often relapsed when the infusion was discontinued, hence, the idea of continuous intravenous therapy until the danger of relapse had passed. In the first year he reported 30 cases of very severe diarrhea, with only 7 deaths, and the following year 53 cases, with only 6 deaths, a marked improvement on the mortality rates that prevailed at that time. In 1934 Lyon and others<sup>8</sup> reported 821 cases of diarrhea treated at Cincinnati General Hospital from 1923 to 1932, with a mortality rate of 32.4 per cent. They also described the use of continuous intravenous therapy, as outlined by Karelitz, on 17 severely ill patients, of whom 8 died; some of these patients were also suffering from pneumonia. Cohen and others<sup>9</sup> recorded their experience in 1933 with continuous intravenous treatment, and also extensive chemical determinations on blood, urine, and stools during the period of the diarrhea. Their series included 9 patients, of whom 2 died (2 had concomitant otitis media, and 2 had pneumonia).

More recently, several series of cases have been reported from England. Much of the diarrhea was thought to be secondary to parenteral infection and in most series the death rate was exceedingly high. Smellie<sup>10</sup> reported 500 cases in Birmingham, England, with 240 (48 per cent) deaths. Of these, 321 had some type of parenteral infection. Campbell and Cunningham<sup>11</sup> reported 574 cases of diarrhea from London during the period January, 1937 through August 1939. They divided their cases into "dehydrated" and "non-dehydrated"; in the first group there were 152 deaths in 283 cases (53.7 per cent); in the second, 7 deaths in 291 cases (2.4 per cent). They noted a 30.5 per cent incidence of parenteral infection. Their therapy consisted of starvation for twenty-four to forty-eight hours, giving clear fluids orally or continuous subcutaneous Ringer's glucose-saline. From Britain again there is a report by Field and others<sup>12</sup> in 1943, citing 100 cases with 23 deaths (23 per cent). For marked dehydration they employed continuous intravenous Hartmann's solution for twenty-four hours, and then instituted a "pyloric feeding schedule." It is interesting to note that the British authors who employ continuous intravenous therapy use mainly Hartmann's solution, Ringer's solution, or normal saline.

The outstanding British paper as far as successful therapy is concerned is a report in 1944 by Alexander and Eiser from London.<sup>13</sup> They describe 150 cases of children under 15 months of age, with only 8 deaths. The series includes 88.6 per cent of patients with evidence of parenteral infection, chiefly otitis media and mastoiditis. Their therapy consisted of sulfathiazole and clear fluids for twelve to twenty-four hours, followed by dilute feedings in the milder cases; the severer, dehydrated cases were given intravenous fluids, alternating with half-strength plasma (diluted with Hartmann's solution) and Hartmann's solution, until the patients were able to take oral fluids. Of these cases, only 69 were dehydrated; all the deaths were in this group. If we take of these cases only the dehydrated ones as comparable to those in our series the mortality

rate becomes practically 12 per cent. Finally, there are 215 cases from Middlesex, England, reported by Gairdner<sup>14</sup> in 1944, with 109 deaths (51 per cent). Thirty-five per cent of these patients had parenteral infections. The death rate was the same in those without or those with parenteral infection. Continuous intravenous therapy was employed in the more acutely ill patients, but the author's comment is that "it could be relied on to correct dehydration, but only too often failed to save life."

Two recent reports from the United States present encouraging statistics on the results of present-day therapy of infantile diarrhea. From Louisville in 1944 Glaser and Bruce<sup>15</sup> reported 180 cases seen from 1940 to 1942, with 32 deaths (17.8 per cent); in 1942 there were 6 deaths in 58 cases, a death rate of only a little over 10 per cent. Their therapy includes continuous intravenous fluids for thirty-six hours in the more severely ill patients, followed by oral feedings of low calorie formula every three to four hours, allowing the infant to regulate his intake at will. This regime, without the intravenous fluids, is used on the milder cases also, after an initial twelve hours of starvation. All patients received sulfonamide. Govan and Darrow<sup>16</sup> during the summer of 1945 were able to achieve the remarkably low "corrected mortality rate" of 6 per cent in 50 consecutive patients treated by a new plan in which various procedures used in one place or another during the past twenty years are employed, but potassium chloride is added to the solutions containing sodium chloride, sodium lactate and glucose. In all severely ill patients, blood or plasma infusions are also carried out. Before the institution of this method of therapy the "corrected mortality rate" of 53 consecutive patients had been 32 per cent. It will be of interest to see whether the marked improvement which occurred with the introduction of the new method of therapy is maintained in following years.

#### SUMMARY

The morbidity and mortality of diarrhea still remain high in Cincinnati. Artificial feeding, poverty, poor sanitary facilities, and ignorance appear at least in part responsible for the high incidence of the disease. Specific infection with dysentery and related bacilli accounts only for a small percentage of cases. Parenteral infection also plays an unimportant role in the causation of severe diarrhea. Compared with previous experience a low death rate has been achieved for the past two years at the Cincinnati General Hospital by the use of consistent, planned, continuous, intravenous therapy. In 292 infants and children admitted to the hospital seriously ill with diarrhea the death rate was 7.6 per cent. Two hundred and twenty-one of these patients were infants under one year of age. Here the death rate was 9.1 per cent. The "corrected case fatality rate" for the series was 5.6 per cent.

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## PENICILLIN AS AN AID IN THE TREATMENT OF PRIMARY STAPHYLOCOCCUS PNEUMONIA WITH EMPYEMA

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PRIOR to the advent of penicillin as a therapeutic agent, the reported mortality of staphylococcal infection of the pleural cavity ranged from 22 to 100 per cent. Riley,<sup>1</sup> in 1944, reported fifteen patients treated with sulfonamides, staphylococcal antitoxin, and a bacteriophage, with a mortality of 40 per cent. In a group of twenty-two infants under one year of age treated by various surgical methods, there were eight fatalities (36 per cent), and of seven children over one year of age, two died (28 per cent). Hoehberg and Kramer,<sup>2</sup> in 1939, reported thirty-three patients treated by surgical methods with a gross mortality of 22 per cent. Ladd and Swan,<sup>3</sup> in 1943, pointed out the significance of age as a prognostic factor when they reported a mortality of 66 per cent in twelve infants under 4 months of age in contrast to a mortality of 5 per cent in twenty-one children of over 4 months. These patients were treated with surgical methods alone. In 1942, Clemens and Weems reported six cases of primary staphylococcal pneumonia. All of the patients had empyema and four of them had a pyopneumothorax. The mortality was 100 per cent and the authors felt that the overwhelming toxemia was the main factor in the cause of death. A short time ago Philips and Kramer<sup>4</sup> reported five cases of staphylococcal infection of the lung and pleural cavity in infants less than 3 months of age. One patient, moribund on admission, died within eighteen hours, and autopsy showed multiple lung abscesses without evidence of empyema. Of the four who survived, two received both intrapleural and intramuscular penicillin and two received only intrapleural penicillin. Thoracotomy and rib resection were required in two cases. The improvement in mortality was attributed largely to the addition of penicillin to other therapeutic methods.

Between 1929 and 1944, eight children with primary staphylococcal pneumonia and empyema were admitted to Strong Memorial Hospital. Two of these patients (25 per cent) died. Of the remaining six, two were treated by aspiration and trocar drainage only; two others were treated with sulfonamide, aspiration, and staphylococcal antitoxin; two received only multiple aspirations. All recovered. The average period of hospitalization was 38.5 days, the longest admission being 79 days and the shortest, 6 days. Judging from these cases, one might assume that there is a marked variation in the virulence of the infecting organism or a marked variation in the individual immune response. Age did not seem to be an influencing factor.

Seven children with staphylococcal pneumonia and empyema were recently admitted to Strong Memorial Hospital. All were treated by both intrapleural and intramuscular injections of penicillin. In reviewing the literature, it was



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showed marked decrease in the size and density of the cavity. The patient was discharged on the twenty-eighth hospital day. X-rays two weeks later showed thickened pleura and accentuated markings at the left base. No fluid was present.

CASE 2.—H. B., an 11-year-old boy, was admitted Jan. 10, 1945, with chest pain, fever, and loss of appetite. Six days before admission he had a sore throat, chest pain, difficulty in breathing, and a cough productive of mucoid sputum which was not blood tinged. He was nauseated and vomited several times. His physician diagnosed pleurisy and prescribed sulfathiazole, 1.0 Gm. every four hours. Four days before admission the patient noted a generalized erythematous rash and a sore tongue. The next day the sulfathiazole was discontinued and sulfadiazine given. The rash faded rapidly but the chest pain, fever, and anorexia became more marked.

On admission, physical examination showed a well-developed, 11-year-old boy with a temperature of 39.7° C., who was severely ill. His respirations were labored and rapid with an expiratory grunt and splinting of the left chest. There was a profuse, mucopurulent, nasal discharge. The left chest was resonant to percussion above the fourth rib anteriorly and the second rib posteriorly, with a few râles in these areas; below this there was flatness to percussion with absent breath sounds. The right chest was normal. The abdomen was moderately tender in both upper quadrants. The spleen was not palpable.

Laboratory studies on admission showed the following: red blood cells, 4,250,000; hemoglobin, 14.0 Gm.; white blood cells, 12,150; differential smear, polymorphonuclears 69 per cent, lymphocytes 14 per cent, myelocytes 12 per cent, eosinophiles 5 per cent. The urine was normal. Blood sulfadiazine level was 3.3 mg. per 100 c.c. Cultures from the nose and throat yielded *Str. viridans* and a yeast; no pneumococci were recovered from the mouse inoculation. Blood culture was sterile. X-rays of the chest showed a left hydrothorax with no definite area of pneumonic infiltration.

Course.—Thoracentesis yielded 200 c.c. of turbid fluid. Gram stains of the sediment of this fluid showed gram-positive cocci, but the cultures were sterile. The boy was given 1.0 Gm. sulfadiazine every four hours. On the third hospital day, intramuscular injection of 5,000 units of penicillin every three hours was started. This dosage was doubled the next day and eight days later it was increased to 15,000 units every two hours when a favorable response was not apparent. Daily, for fourteen days, 100 to 350 c.c. of turbid straw-colored fluid were removed from the chest and 15,000 units of penicillin were injected. Cultures of the fluid from the fifth and sixth thoracentesis yielded hemolytic *Staph. aureus*, although the smears were negative. Repeated blood cultures during this period were sterile. He continued to run a septic course showing little improvement. Sulfadiazine was discontinued after one week of administration. On the fourteenth thoracentesis, pus was encountered in the seventh interspace in the posterior axillary line immediately after the usual turbid fluid had been obtained one interspace higher. This pus showed many gram-positive cocci on smear and hemolytic *Staph. aureus* on culture. Trocar drainage was instituted, the cavity was irrigated daily, and 15,000 units of penicillin were instilled with the tube clamped off for several hours. Sulfathiazole was given in doses of 1.25 Gm. every four hours; the highest blood level obtained was 8.7 mg. per 100 c.c. Following trocar drainage, the patient's condition improved gradually and he remained afebrile. Local penicillin was discontinued on the twenty-third hospital day and cultures of the empyema fluid were negative three days later. On the forty-eighth day the tube was removed, following which the sinus closed rapidly. The patient showed slight daily temperature elevations when first allowed out of bed, but was well when discharged on the fifty-seventh hospital day. X-rays taken one week later showed the lung fields to be essentially normal with residual adhesive pleuritis at the left base.

CASE 3.—E. K., a 20-month-old white girl, was admitted Jan. 11, 1945, with a chief complaint of abdominal pain. One week before admission she developed an upper respiratory infection characterized by coryza and a nonproductive cough, followed by anorexia. The night before admission she vomited twice and complained of severe, generalized, abdominal pain. On the morning of admission the temperature was 104° F. A physician was called who found tenderness in the right lower quadrant of the abdomen and advised hospitalization.

noted that reports on this method of treatment of primary staphylococcal pneumonia with empyema in children were relatively scarce. Consequently, it was felt that even though the present series is quite small, a description of the plan of treatment and the results obtained is warranted.

#### CASE REPORTS

CASE 1.—R. B., an 18-day-old infant, was admitted May 17, 1944, with a chief complaint of fever. Several days after birth she had had mild diarrhea and two episodes of cyanosis. A presumptive diagnosis of congenital heart disease had been made. She had been discharged from the nursery on the eighth day of life in good condition. After that there had been only one episode of cyanosis. Two days before admission the formula was changed and one drop of a 1:1,000 solution of atropine was added to alternate feedings because of hypertonicity and frequent vomiting. The day preceding admission she was irritable, vomited, and choked on her 6 A.M. feeding. In the afternoon she developed a temperature of 103.5° F. She had received one drop of atropine in her 10 A.M. feeding.

Physical examination on admission revealed a well-developed, well-nourished infant, acutely ill with a temperature of 38.5° C. The lungs were clear. The heart was not enlarged but there was a systolic blow over the precordium. The tip of the spleen was palpable and the liver was felt one fingerbreadth below the costal margin.

Laboratory studies on admission showed the following: red blood cells, 3,400,000; hemoglobin, 14.5 Gm.; white blood cells, 13,000, with polymorphonuclears 70 per cent, lymphocytes, 26 per cent, and monocytes, 4 per cent. The urine contained a trace of albumin. Hemolytic *Staphylococcus aureus*, *Escherichia coli*, and *Streptococcus viridans* were isolated from the nose and throat. No pneumococci were recovered from the mouse inoculation. In the blood culture, hemolytic *Staphylococcus albus* grew in the broth but not in the plates. Roentgenograms showed no evidence of pneumonia.

Course.—The child received sulfadizine, 0.25 Gm. stat. and 0.125 Gm. every six hours; the fever persisted. On the second hospital day she was cyanotic, and there were râles over the left chest but no dullness to percussion. The following day a flat percussion note with suppression of breath sounds and fine râles was present over the entire left chest. Her condition became worse and she was placed in an oxygen tent. Thoracentesis yielded 0.5 c.c. of serosanguineous fluid, from which hemolytic *Staph. aureus* was isolated. The child's condition improved slowly but she remained febrile. Three transfusions of whole blood were given. The sulfadiazine was discontinued after ten days. On the fifteenth hospital day, thoracentesis yielded 4 c.c. of bloody fluid, culture of which was sterile. The white blood count remained elevated; suppressed breath sounds, tubular breathing, and fine râles persisted over the left chest. On the following day the intramuscular injection of 2,000 units of penicillin every two hours was started and continued for ten days. The temperature dropped to normal and remained so until the child was discharged on June 16, thirty days after admission.

On June 30, 1944, the infant was readmitted with a complaint of gradually increasing cough for six days without fever. Physical examination revealed dullness to percussion, fine râles, and suppressed breath sounds over the left chest. The cardiac murmur had disappeared.

Laboratory studies on admission showed the following: red blood cells, 3,650,000; hemoglobin, 10 Gm.; white blood cells, 21,600 with polymorphonuclears 56 per cent, and lymphocytes 44 per cent. Hemolytic *Staph. aureus* and *Str. viridans* were grown from the nose culture; no pneumococci were recovered from the mouse inoculation. X-ray showed a localized collection of fluid in the left lower chest.

The child remained afebrile throughout. On the day of admission, 30 c.c. of thick green pus were aspirated from the left chest and 10,000 units of penicillin were injected into the empyema space. Hemolytic *Staph. aureus* was cultured from the pus. The next day, 3 c.c. of pus were aspirated, and 5,000 units of penicillin were injected. On the next five successive days, no fluid was obtained on thoracentesis. During the first twenty-four hospital days, 2,000 units of penicillin were injected intramuscularly every three hours, and two transfusions of whole blood were given. X-rays of the chest seven days and twenty-four days after admission

showed marked decrease in the size and density of the cavity. The patient was discharged on the twenty-eighth hospital day. X-rays two weeks later showed thickened pleura and accentuated markings at the left base. No fluid was present.

CASE 2.—H. B., an 11-year-old boy, was admitted Jan. 10, 1945, with chest pain, fever, and loss of appetite. Six days before admission he had a sore throat, chest pain, difficulty in breathing, and a cough productive of mucoid sputum which was not blood tinged. He was nauseated and vomited several times. His physician diagnosed pleurisy and prescribed sulfathiazole, 1.0 Gm. every four hours. Four days before admission the patient noted a generalized erythematous rash and a sore tongue. The next day the sulfathiazole was discontinued and sulfadiazine given. The rash faded rapidly but the chest pain, fever, and anorexia became more marked.

On admission, physical examination showed a well-developed, 11-year-old boy with a temperature of 39.7° C., who was severely ill. His respirations were labored and rapid with an expiratory grunt and splinting of the left chest. There was a profuse, mucopurulent, nasal discharge. The left chest was resonant to percussion above the fourth rib anteriorly and the second rib posteriorly, with a few rales in these areas; below this there was flatness to percussion with absent breath sounds. The right chest was normal. The abdomen was moderately tender in both upper quadrants. The spleen was not palpable.

Laboratory studies on admission showed the following: red blood cells, 4,250,000; hemoglobin, 14.0 Gm.; white blood cells, 12,150; differential smear, polymorphonuclears 69 per cent, lymphocytes 14 per cent, myelocytes 12 per cent, eosinophiles 5 per cent. The urine was normal. Blood sulfadiazine level was 3.3 mg. per 100 c.c. Cultures from the nose and throat yielded *Str. viridans* and a yeast; no pneumococci were recovered from the mouse inoculation. Blood culture was sterile. X-rays of the chest showed a left hydrothorax with no definite area of pneumonic infiltration.

Course.—Thoracentesis yielded 200 c.c. of turbid fluid. Gram stains of the sediment of this fluid showed gram-positive cocci, but the cultures were sterile. The boy was given 1.0 Gm. sulfadiazine every four hours. On the third hospital day, intramuscular injection of 5,000 units of penicillin every three hours was started. This dosage was doubled the next day and eight days later it was increased to 15,000 units every two hours when a favorable response was not apparent. Daily, for fourteen days, 100 to 350 c.c. of turbid straw-colored fluid were removed from the chest and 15,000 units of penicillin were injected. Cultures of the fluid from the fifth and sixth thoracentesis yielded hemolytic *Staph. aureus*, although the smears were negative. Repeated blood cultures during this period were sterile. He continued to run a septic course showing little improvement. Sulfadiazine was discontinued after one week of administration. On the fourteenth thoracentesis, pus was encountered in the seventh interspace in the posterior axillary line immediately after the usual turbid fluid had been obtained one interspace higher. This pus showed many gram-positive cocci on smear and hemolytic *Staph. aureus* on culture. Trocar drainage was instituted, the cavity was irrigated daily, and 15,000 units of penicillin were instilled with the tube clamped off for several hours. Sulfathiazole was given in doses of 1.25 Gm. every four hours; the highest blood level obtained was 8.7 mg. per 100 c.c. Following trocar drainage, the patient's condition improved gradually and he remained afebrile. Local penicillin was discontinued on the twenty-third hospital day and cultures of the empyema fluid were negative three days later. On the forty-eighth day the tube was removed, following which the sinus closed rapidly. The patient showed slight daily temperature elevations when first allowed out of bed, but was well when discharged on the fifty-seventh hospital day. X-rays taken one week later showed the lung fields to be essentially normal with residual adhesive pleuritis at the left base.

CASE 3.—E. K., a 20-month-old white girl, was admitted Jan. 11, 1945, with a chief complaint of abdominal pain. One week before admission she developed an upper respiratory infection characterized by coryza and a nonproductive cough, followed by anorexia. The night before admission she vomited twice and complained of severe, generalized, abdominal pain. On the morning of admission the temperature was 104° F. A physician was called who found tenderness in the right lower quadrant of the abdomen and advised hospitalization.

Physical examination on admission showed a severely ill infant with a temperature of 39.6° C. Her respirations were rapid with an occasional expiratory grunt. There was minimal inspiratory lag on the left side of the chest with dullness to percussion, decreased breath sounds, and fine râles over the left base. The abdomen was not distended but there was slight resistance and tenderness to deep palpation in the right upper quadrant. The spleen was not palpable.

Laboratory studies on admission showed the following: red blood cells, 3,960,000; hemoglobin, 10.3 Gm.; white blood cells, 17,600; polymorphonuclears, 83 per cent and lymphocytes, 17 per cent. Blood culture showed *Staph. albus* in the broth but no growth in the plates. Nose and throat culture yielded no pathogens. Hemolytic *Staph. aureus* was recovered from the mouse inoculation, but no pneumococci were found. A roentgenogram of the chest showed bronchopneumonia at the left base.

*Course.*—The patient was treated with parenteral fluids and sulfadiazine, 0.250 Gm. every four hours. The following morning the area of dullness at the left base had increased slightly and the temperature remained elevated. On the second hospital day, examination of the chest showed the presence of fluid and this was confirmed by x-ray. Thoracentesis yielded 1 c.c. of fluid which on smear showed occasional gram-positive cocci and on culture grew hemolytic *Staph. aureus* which was coagulase-positive. A transfusion of whole blood was given. On the third hospital day she appeared extremely ill and had labored respirations, and the spleen became palpable. The dosage of sulfadiazine was increased although the level in the blood was 10.8 mg. per 100 c.c. She received fluids by vein and was placed in an oxygen tent. Five days after admission the level of fluid in the chest was higher and two thoracenteses were performed with the removal of 60 c.c. of thick, reddish-brown pus. 20,000 units of penicillin were instilled into the pleural space following each thoracentesis and intramuscular penicillin was begun, 10,000 units for two doses and then 5,000 units every three hours. She was also given plasma and parenteral fluids. Daily thoracenteses were performed with the removal of 15 to 95 c.c. of pus and instillation of 20,000 units of penicillin. Her condition improved gradually and x-rays showed progressive localization of the fluid. Sixteen days after admission trocar drainage was instituted and constant suction applied. The empyema cavity was irrigated frequently with normal saline and Dakin's solution. Three weeks after admission, penicillin and sulfadiazine were discontinued in spite of positive cultures from the pleural fluid as the empyema cavity was well walled off and there was no evidence of an active pneumonic process. Pantopaque injections of the cavity on the thirty-sixth and forty-eighth hospital days showed progressive diminution in its size. Two weeks after chemotherapy was discontinued, cultures of the empyema drainage were sterile. Ten days later, the catheter was removed and the sinus tract closed gradually. Fifty days after admission the sinus tract was entirely healed, and x-rays showed re-expansion of the lungs with clear parenchyma and slight pleural thickening over the left base.

CASE 4.—G. B., a 6-month-old boy, was admitted Feb. 24, 1945, with a chief complaint of fever and grunting respirations. Two weeks before admission he developed an upper respiratory infection and later had a mild cough. The day before entry he vomited once, became irritable, and had fever and grunting respirations.

Physical examination showed a well-developed, well-nourished but pale and acutely ill infant with a temperature of 39.3° C. There was a mucopurulent nasal discharge and the pharynx showed moderate injection. There was slight dullness to percussion at the left base, but no râles or changes in the breath sounds were heard.

Laboratory studies on admission showed the following: red blood cells, 4,500,000; hemoglobin, 14.5 Gm.; white blood cells, 17,000; polymorphonuclears, 91 per cent, lymphocytes, 8 per cent, and monocytes, 1 per cent. Nose and throat cultures yielded *Staph. albus* and *Neisseria catarrhalis*. Blood culture was sterile. X-rays showed a hazy mottled density at the left base and elevation of the left diaphragm.

*Course.*—The patient was given sulfadiazine, 0.315 Gm. every four hours. He continued to have a spiking fever. Sulfadiazine blood levels were between 13.2 and 15.1 mg. per 100 c.c.

On the third day after admission there was definite splinting of the left chest with flatness to percussion and absent breath sounds. The administration of oxygen and intramuscular injection of penicillin, 10,000 units stat. and 5,000 units every three hours were started. A nose and throat culture showed hemolytic *Staph. aureus*. Thoracentesis yielded 10 c.c. of sanguineous purulent fluid which showed gram-positive cocci on smear. Thoracenteses were performed daily and 15,000 units of penicillin were injected into the pleural space. His condition improved, the respirations became easier, and the temperature returned to normal. Smears and cultures of the pleural fluid continued to show hemolytic *Staph. aureus*. On the thirteenth hospital day, trocar drainage was instituted and followed by continuous suction. Fifteen days after admission sulfadiazine was stopped, and two days later the intramuscular injection of penicillin was discontinued. Cultures of the pleural fluid continued to show hemolytic *Staph. aureus*. On the forty-fourth hospital day the local penicillin, which had been discontinued following insertion of the catheter into the chest, was again given for one week. One week later drainage from the cavity was minimal and on pantopaque visualization the cavity was seen to lie posteriorly in the mid-lung zone with normal surrounding parenchyma. On the fifty-fourth day the child's temperature rose and considerable purulent material was aspirated from the chest which yielded hemolytic *Staph. aureus* on culture. Also at this time bilateral myringotomy was performed because of tense, injected drums. Local penicillin and oral sulfadiazine were reinstituted and continued for one week. Two days after these were discontinued the catheter slipped out and was not replaced. The sinus closed rapidly and there was no drainage five days later. At this time the area occupied by the empyema cavity was clear except for increased lung markings and thickened pleura. He was discharged on the sixty-seventh hospital day, and two weeks later x-ray revealed only slight pleural thickening.

CASE 5.—S. W., a 2½-year-old girl, was admitted Feb. 27, 1945, referred with a diagnosis of "pneumonia or appendicitis." One week before admission she developed croup which responded well to sulfadiazine. The day before admission she again had fever, became restless, and had grunting respirations. Sulfadiazine was given, and she received a total of 1.75 Gm. without improvement. On the morning of admission she developed moderately severe abdominal pain without nausea, vomiting, or diarrhea.

Physical examination on admission revealed a well-nourished, acutely ill child with a temperature of 39.3° C. Her skin was hot and dry. She had a profuse purulent nasal discharge and exudate on the tonsils.

Her respirations were irregular and grunting. The percussion note over the right base posteriorly was flat and there was suppression of breath sounds with many fine râles heard over this area. There was voluntary spasm and tenderness to palpation in the right upper quadrant of the abdomen.

Laboratory studies on admission showed the following: red blood cells, 5,360,000; hemoglobin; 14.5 Gm.; white blood cells, 18,650, with polymorphonuclears, 84 per cent, lymphocytes, 14 per cent, and monocytes, 1 per cent. Hemolytic *Staph. aureus* and pneumococci types IV and VI were cultured from the throat. The blood culture was sterile. The blood sulfadiazine level on admission was 10.1 mg. per 100 c.c. X-ray of the chest showed a pneumonic consolidation at the right base.

Course.—She received sulfadiazine, 1.95 Gm. per day, and parenteral fluids. The next day she was cyanotic during coughing spells. Her temperature remained elevated. There was an increase in the amount of consolidation in the right lower lobe and a small pleural effusion was present. Penicillin, 7,500 units, was then administered every three hours. Thoracentesis on the right yielded 40 c.c. of thick pus from which hemolytic *Staph. aureus* was cultured. 20,000 units of penicillin were instilled into the pleural cavity. Following this, the empyema cleared rapidly. Two days after admission, 15 c.c. of pus were obtained on thoracentesis, and the following day, 3 c.c.; both times, cultures yielded hemolytic *Staph. aureus*. Penicillin was given intrapleurally with each thoracentesis. Nine days after admission no fluid was obtained from the chest. Her improvement after the first week was steady and rapid. She was discharged three and one-half weeks after admission. X-rays showed only residual pleural thickening.

CASE 6.—R. A., a 2-month-old, white male, was admitted on April 15, 1945, with a chief complaint of a cough and cold. He was apparently well until the day before admission, when he developed a mild cough. On the day of admission he developed rapid respirations and refused his food. A twin brother was said to be in good health.

Physical examination on admission showed a well-developed baby with a temperature of 36.5° C. and with rapid, shallow, gasping respirations. His skin was icteric and cold. The extremities were cyanotic and the fontanelle was slightly depressed. The chest showed a lag on the right side with suprasternal retractions. There was flatness to percussion over the right base and in the axilla. Fine, moist, crackling râles were heard over both lung fields, but were more marked on the right. The liver was felt one fingerbreadth below the costal margin and the spleen, two fingerbreaths.

Laboratory studies on admission showed the following: red blood cells, 2,400,000; hemoglobin, 8.5 Gm.; white blood cells, 22,300, with polymorphonuclears, 44 per cent, lymphocytes, 44 per cent, monocytes, 3 per cent, and juvenile forms, 9 per cent. Blood culture was sterile. A nose and throat culture revealed a predominance of hemolytic *Staph. aureus*; no pneumococci were recovered from the mouse inoculation. X-ray revealed compensatory emphysema of the left lung, poor aeration of the right lung with prominent root markings, and many small parenchymal infiltrations. No fluid was visualized.

Course.—The patient received 15,000 units of penicillin intramuscularly, immediately followed by 5,000 units every three hours, 0.25 Gm. of sodium sulfadiazine intravenously, and 0.25 Gm. every six hours thereafter by mouth. He received parenteral fluids including hypertonic glucose and whole blood, and was placed in an oxygen tent. Three hours after admission he became apneic but rallied after receiving caffeine sodium benzoate and artificial respiration. During the next twenty-four hours his color improved slightly but his temperature rose to a maximum of 40.2° C. and was only slightly lowered by aspirin and tepid sponges. He then developed abdominal distention and accentuated respiratory difficulty. His course continued steadily downhill and despite restorative measures he expired thirty-six hours after admission.

At autopsy the left pleural cavity contained a trace of clear, straw-colored fluid, and the parietal surfaces were clear. The right pleural cavity contained approximately 10 c.c. of thick, dark, purulent fluid. The left lung was of normal size; the upper lobe was emphysematous, while the lower lobe contained a large, firm, consolidated area which on section had a reddish gray color and showed a few small abscesses filled with creamy pus. The surface of the right lung showed many small, blisterlike areas filled with creamy, yellow pus, and the bronchi were reddened and filled with exudate. The lung sank quickly in water and was extensively consolidated in all areas. Microscopically, the heavily consolidated areas showed white cells and fibrin in the alveoli and bronchi with severe necrotization, abscess formation, and some hemorrhage. Over these areas there was a thick fibrinopurulent pleural exudate with many bacteria. Smears of the pus and empyema fluid showed many gram-positive cocci in clusters, and cultures were positive for hemolytic *Staph. aureus*. The diagnosis of empyema was not made during life.

CASE 7.—S. K., a 31-month-old boy, was admitted July 19, 1945, with a chief complaint of heavy breathing. Ten days before admission he developed a cough and cold without fever. On the day preceding admission his respirations became labored and grunting, his temperature rose to 103° F., and he took fluids poorly. On the morning of admission he was taken to another hospital where an x-ray of the chest was taken and interpreted as negative. His white count was 10,000. An unsuccessful lumbar puncture was attempted because of a slightly stiff neck. He was sent home and given sulfadiazine, receiving a total of 1.0 Gm. before admission. Late in the evening he suddenly became cyanotic after administration of his medication and was brought immediately to the hospital.

Examination on admission showed an acutely ill 31-month-old child with a temperature of 39.2° C. His respirations were rapid and shallow with an expiratory grunt. There was minimal subcostal retraction without lag or splinting of the chest. The lungs were resonant to percussion with slightly decreased breath sounds over the right lower lobe and loud, harsh

breath sounds over the left lower lung field, without rales. The abdomen was slightly distended but otherwise normal.

Laboratory studies on admission showed the following: red blood cells, 4,500,000; hemoglobin, 12.1 Gm.; white blood cells, 19,200, with polymorphonuclears, 65 per cent, lymphocytes, 31 per cent, monocytes, 2 per cent eosinophiles, 1 per cent, and basophiles, 1 per cent. The sulfadiazine level of the blood was 6.0 mg. per 100 c.c. Nose and throat cultures showed hemolytic *Staph. aureus*; no pneumococci were recovered from the mouse inoculation. X-ray revealed conglomerate shadows in the left lower lung which were interpreted as early bronchopneumonia.

Course.—The patient received parenteral fluids and sulfadiazine, 1.25 Gm. per day. On the morning after admission, because of the continued high fever, the progression of signs in the lung, and the finding of hemolytic *Staph. aureus* in the nose and throat cultures, penicillin was started and the patient was placed in an oxygen tent. Two days after admission the respiratory embarrassment was more marked and there was definite evidence of fluid in the left chest. X-ray showed fluid to the level of the fifth rib posteriorly and increased density in the lung fields, due partly to overlying fluid and partly to definite parenchymal infiltration. Two thoracenteses were performed on the second hospital day with the removal of thick, purulent fluid and instillation of 15,000 units of penicillin into the cavity. Progressively smaller amounts of empyema fluid were removed each day. Penicillin was instilled into the pleural cavity following each thoracentesis. He also received 10,000 units of penicillin every three hours intramuscularly. Supportive measures consisted of several transfusions of whole blood and parenteral Vitamin B complex. On the nineteenth hospital day, cultures of the thoracentesis fluid showed no growth although occasional cocci were seen on three subsequent smears. On the sixteenth hospital day intramuscular penicillin was discontinued but was started again thirty-six hours later because of the presence of a shadow in the left upper lung suggesting pneumonic infiltration, and was continued for sixteen days. On the seventeenth hospital day no fluid was obtained upon thoracentesis and further taps were not done. The patient was discharged thirty-seven days after admission, afebrile and in excellent condition. The X-ray at this time showed slight, residual, pleural thickening at the left base.

#### COMMENT

It is evident that the plan of therapy varied considerably between the times the first and last cases were treated. Case 1 received relatively small doses of penicillin for rather short periods. Only on the second admission was it given intrapleurally. Case 7 was given larger doses for a longer period. It is now thought that 15,000 to 25,000 units should be given intramuscularly every three hours, even to infants, and that larger doses are probably unnecessary. A thoracentesis should be done each day, as much fluid should be removed as possible, and from 30,000 to 50,000 units of penicillin should be instilled. For older children as much as 50,000 to 75,000 units should be given intrapleurally each day. As Cooke and Goldring<sup>17</sup> have shown, high levels can be maintained in the pleural fluid by giving penicillin once daily into the pleural space and every 3 hours intramuscularly.

Cultures of the pleural fluid rapidly become "sterile" although smears continue to show gram-positive cocci for a varying length of time. One should not be led into a false sense of security by such "sterile" cultures, but rather should make daily smears and continue the administration of both intrapleural and intramuscular penicillin for at least one to two weeks after organisms can no longer be found by smear. It may be discontinued then unless there is further indication for continued administration.



Sulfonamide therapy should be instituted as soon as possible and blood levels of 12 to 15 mg. per cubic centimeter should be maintained. Several observers<sup>18-20</sup> have pointed out a synergistic action when sulfonamides and penicillin are given together, although others<sup>21</sup> do not agree with this.

Frequent small blood transfusions during the acute stages are beneficial as most infants have a moderately severe anemia with the infection. They are also of value in that they furnish fresh complement. It has been shown that infants normally have low titers of complement and also that the titer drops during acute infections.

Additional supportive therapy includes the maintenance of an adequate intake of food, fluids, and vitamins, especially members of the B complex. Oxygen should be administered when necessary.

In some instances various surgical procedures must be performed. Cases in which this becomes necessary are those in which loculation has occurred and isolated pockets of pus have formed. All of these are not accessible to the needle or to chemotherapy, and surgical drainage may have to be employed. This localization was exemplified in Case 2 where an isolated pocket was encountered on the fourteenth thoracentesis. When the fluid continues to accumulate, and cultures or smears remain positive, trocar drainage with constant or intermittent suction, and irrigation with Dakin's or some other suitable solution may be required.

All cases should be followed closely by x-ray and fluoroscopy and by repeated physical examination. One should watch for other foci of staphylococcal infection.

#### CONCLUSION

1. Seven cases of primary staphylococcal pneumonia with empyema are presented. The mortality rate was 14 per cent; the infant who expired, died thirty-six hours after admission.

2. Treatment consisted of the administration of relatively large doses of penicillin intramuscularly and directly into the pleural space, and of moderately large amounts of sulfonamide by mouth. Supportive treatment included blood transfusions and maintenance of a good state of nutrition.

3. Patients should be followed closely by x-ray and fluoroscopy and by repeated physical examination. Surgical drainage should be instituted when indicated.

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## THE A-B BLOOD GROUPS AND Rh-Hr BLOOD TYPES IN CONGENITAL ATHETOSIS

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ONE of the syndromes attributed to defects of the basal ganglia is congenital athetosis. The etiology of this condition is generally obscure, but recent studies in a group of athetotic patients with kernicterus have clarified the mechanism.

Kernicterus occurs almost exclusively in patients who have had icterus gravis,<sup>1-4</sup> a severe and highly fatal antigen-antibody disease,<sup>6</sup> during the neonatal born period. This condition is probably brought about by intravascular agglutination or conglutination,<sup>4, 5</sup> often associated with intravascular hemolysis of the infant's red blood cells by an antibody which is manufactured by the mother and is transferred across the placental membrane to the infant. While sensitization of an Rh-negative woman by an Rh-positive fetus accounts for the bulk of the cases,<sup>6</sup> sensitization to the A-B factors can also give rise to the disease.<sup>4</sup>

There is evidence that the bile staining of the basal ganglia (hence the name kernicterus) is secondary to cellular injury and that the pigmentation occurs in the same way that intravital dyes generally localize in zones of injury.<sup>2, 4, 5</sup>

In order to determine whether or not isosensitization might explain other instances of congenital athetosis, the various blood factors (A, B, M, N, Rh, Hr) were studied in a group of children with this condition. Where the mother's blood belonged to type rh\* (Rh negative), studies of her blood serum were made for agglutinins and glutinins against Rh-positive cells.†

The group studied consisted of twenty-three children with athetosis beginning early in life. The cases were assembled at the Institute for Crippled and Disabled Children, New York, and at the Ridgewood Branch of Hackensack Hospital Orthopedic Clinic, through the courtesy and kind cooperation of Dr. George Deaver to whom we wish to express our appreciation. The patients ranged from 1 to 26 years of age, nine being male and fourteen female. Labor was difficult in fifteen of twenty-three cases; in two it was precipitate, in four it was premature, and in three it was normal. There were three twin births. The postnatal course was stormy in thirteen cases, normal in nine, and in one the mother was unable to tell whether or not there were any difficulties. The most common postnatal symptom was cyanosis (eight cases); next in frequency was convulsions (seven cases).

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\*Type rh blood gives negative reactions in tests with all three Rh antisera, anti-Rho, anti-Rh', and anti-Rh".<sup>7</sup>

†For the technique of the Rh sensitization tests, see Wiener.<sup>8</sup>

Intelligence quotients were determined in ten of the older children, and the scores ranged from 55 to 114. One girl (not tested) was going to college. Three children aged 2, 5, and 9 years were severely retarded. The remainder appeared to be within the normal range. Estimates of intelligence in children with athetosis are probably too low, because the children have great difficulty in expressing themselves. Moreover, their early training is apt to have been inadequate.

The results of the study are shown in Table I. In only five of the twenty-three mothers was the blood Rh negative, and in none of these were anti-Rh agglutinins or glutinins found in their serum. With regard to the Landsteiner blood groups, in four instances (Cases 6, 14, 15, and 18) the blood group of the patient was incompatible with the mother's blood group. While the maternal alpha and beta isoagglutinins in these cases were not titrated, this incidence of incompatibility (17 per cent) is less than that occurring in normal families (about 25 per cent),<sup>9</sup> and it is, therefore, unlikely that the A-B factors had any bearing on the occurrence of athetosis in our series of cases.

TABLE I. BLOOD GROUPS AND Rh-Hr TYPES IN TWENTY-THREE PATIENTS WITH CONGENITAL ATHETOSIS

CASE	AGE (YR.)	SEX	MOTHER			PATIENT		
			GROUP AND SUB-GROUP	M-N TYPE*	Rh-Hr TYPE†	GROUP AND SUB-GROUP	M-N TYPE	Rh-Hr TYPE
1	20	F	A <sub>1</sub> B	M	Rh <sub>2</sub>	B	M	rh
2	16	M	A <sub>1</sub>	MN	rh	O	MN	rh
3	19	F	A <sub>1</sub>	MN	rh	A <sub>1</sub>	M	Rh, rh
4	20	F	A <sub>2</sub> B	M	Rh, rh	B	MN	Rh, rh
5	26	M	B	MN	Rh <sub>2</sub>	B	MN	Rh <sub>2</sub>
6	17	F	O	MN	Rh, Rh <sub>2</sub>	A <sub>1</sub>	MN	Rh, Rh <sub>2</sub>
7	22	M	B	M	Rh, Rh <sub>2</sub>	O	M	Rh, Rh <sub>2</sub>
8	16	F	A <sub>1</sub>	MN	Rh, Rh <sub>2</sub>	A <sub>1</sub>	M	Rh, Rh <sub>2</sub>
9	17	F	O	MN	rh	O	N	rh
10	20	F	A <sub>1</sub>	M	Rh, rh	A <sub>1</sub>	MN	rh
11	18	F	O	M	Rh, Rh <sub>2</sub>	O	M	Rh, Rh <sub>2</sub>
12	2	F	O	N	Rh, Rh <sub>2</sub>	O	N	Rh, Rh <sub>2</sub>
13	3	F	A <sub>1</sub>	MN	Rh, rh	A <sub>1</sub>	MN	rh
14	2	M	O	MN	rh	A <sub>1</sub>	N	Rh, rh
15	9	F	B	MN	Rh, Rh <sub>2</sub>	A <sub>2</sub>	M	Rh, Rh <sub>2</sub>
16	3	F	A <sub>2</sub>	M	Rh <sub>2</sub>	O	MN	Rh <sub>2</sub>
17	2	F	A <sub>1</sub>	M	Rh, rh	O	M	Rh, rh
18	3	M	O	N	Rh, rh	A <sub>1</sub>	MN	Rh, rh
19	1	F	O	M	Rh, Rh <sub>2</sub>	O	M	Rh, rh
20	5	M	B	MN	Rh, rh	B	MN	Rh, rh
21	3	M	A <sub>1</sub>	M	rh	A <sub>1</sub>	M	Rh, rh
22	3	M	O	MN	Rh, rh	O	MN	Rh, rh
23	4	M	O	M	Rh, rh	O	M	Rh, rh

\*The M-N types are not important clinically, but are included for the sake of completeness.  
†For nomenclature, see Wiener and associates.<sup>7</sup>

The failure of isosensitization to explain the etiology of the bulk of cases of congenital athetosis is to be expected from the case histories and the neurological examinations. In patients with kernicterus there is usually a history of anemia and jaundice in the neonatal period, requiring treatment with repeated transfusions. This is not an invariable rule, however. In some instances the disturbances in the newborn period may be so slight as not to

require even a single transfusion. Convulsions, somnolence, and stupor during the newborn period are common to all athetotics and hence are of no value in differentiating kernicterus from the group as a whole. In kernicterus there is generally severe mental retardation, while in the ordinary athetotic the intelligence is apt to be good. A further differential feature is the health of the subsequent siblings. When a mother has had a child with icterus gravis, subsequent children are invariably erythroblastotic, unless the child happens to be Rh negative like the mother. In the present series, ten mothers had seventeen children after the birth of the affected children. None of the offspring showed erythroblastosis during the neonatal period and none had athetosis.

#### SUMMARY AND CONCLUSIONS

1. The Rh factors were determined in twenty-three patients with congenital athetosis in order to discover whether icterus gravis during the newborn period is an etiologic factor. In only five of the twenty-three patients were the mother's red blood cells Rh negative and in none of these were anti-Rh agglutinins or glutinins found in the mother's serum.

2. The A-B blood group of only four of twenty-three of the patients was incompatible with the maternal serum, an incidence of 17 per cent, which is less than the incidence of incompatibility (25 per cent) found in normal families.

3. These results rule out the Rh and A-B factors as etiologic agents in the bulk of patients with congenital athetosis.

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# FOLLOW-UP STUDY IN RHEUMATIC SUBJECTS PREVIOUSLY TREATED WITH PROPHYLACTIC SULFANILAMIDE

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THE value of sulfonamide prophylaxis in preventing recurrences of active rheumatic fever has been reported by various clinics since 1939. It is important to know also the subsequent course in rheumatic subjects who, having received prophylactic sulfonamide for various periods of time, are observed throughout several years after treatment has been stopped. Some relevant questions on such prophylaxis still need further analysis, such as which age groups and types of rheumatic individuals should best be protected by prophylactic sulfonamide and the length of time this treatment should be maintained.

It was felt that a follow-up study to observe a group of previously treated individuals would be of value. The following report deals with such a follow-up study carried out from 1941 to 1946 in rheumatic individuals all of whom had previously received sulfanilamide prophylaxis while under the care of the Bellevue Children's and Adolescents' Cardiac Clinics between 1939 and 1943. To date, a total of 109 individuals have been treated with sulfanilamide or sulfadiazine in these clinics, forty-five of these are still continuing sulfadiazine. Several patients have moved too far away for continued observation. Of the remaining individuals, sulfanilamide treatment was terminated in the group who are included in this study, allowing an opportunity for making the follow-up observations.

## GROUP STUDIED AND OBSERVATIONS MADE

The follow-up group included fifty-five individuals who were observed throughout a total of 174 patient-years. Seven patients were followed for five years, twenty-two patients for four years, nine patients for three years, seven for two years, and ten for one year. These patients were all personally followed in the clinic at from two- to three-month intervals and more frequently either in the clinic or the hospital when actual or suspected rheumatic activity was noted.

During the 174 patient-years of observation, thirty-nine individuals had no rheumatic recurrences while sixteen developed active rheumatic fever. This represented 158 inactive patient-years in contrast to 16 active patient-years. Of these sixteen cases of rheumatic activity, eight developed in the first year, six in the second year, and two in the third year after prophylactic sulfanilamide had been stopped.

Distribution of years of observation, number and time of recurrences, and length of previous treatment are summarized in Table I. The group of patients who remained free of recurrences and those who developed rheumatic

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activity are compared in respect to factors considered effective in the recurrence pattern of rheumatic fever: past rheumatic history, numbers and severity of attacks, and cardiac diagnoses (Table II); years since last attack (Table III); and ages during the follow-up period (Table IV).

TABLE I. NUMBER AND TIME OF RHEUMATIC RECURRENCES IN RELATION TO YEARS OF PREVIOUS PROPHYLAXIS

	TOTAL	NUMBER OF YEARS OF PREVIOUS PROPHYLAXIS		
		1 YEAR	2 YEARS	3 YEARS
Number of patients	55	22	25	8
Number followed throughout				
5 years	7	6	1	—
4 years	22	8	14	—
3 years	9	3	2	4
2 years	7	1	2	4
1 year	10	4	6	—
Total patient-years of follow-up	174	77	77	20
Number rheumatic recurrences	16	7	4	5*
Year recurrences occurred after stopping therapy				
First year	8	4	3	1
Second year	6	3	1	2
Third year	2	—	—	2

\*Three of these 5 cases had each had three or more attacks of severe carditis, with congestive failure in two instances, prior to the years of prophylactic sulfanilamide.

TABLE II. PAST RHEUMATIC HISTORY AND CARDIAC DIAGNOSIS

	INACTIVE GROUP	ACTIVE GROUP
Total number of patients	39	16
Past rheumatic history		
Total number of attacks	100	44
Per cent of total number of attacks		
Chorea	28%	11%
Polyarthritis, minimal carditis	25%	19%
Moderate to severe carditis ± polyarthritis	47%	70%*
Cardiac diagnoses,†—Per cent of inactive and active groups		
Possible and potential heart disease	30.6%	25.0%
Enlarged heart, mitral insufficiency	13.1%	12.5%
Enlarged heart, mitral insufficiency, mitral stenosis	35.7%	12.5%
Enlarged heart, mitral insufficiency, mitral stenosis, aortic insufficiency	15.5%	16.7%
Enlarged heart, mitral insufficiency, mitral stenosis, aortic insufficiency, aortic stenosis	5.1%	31.3%

\*Congestive failure had been present in two attacks.

†Diagnoses were made according to the Criteria for the Classification and Diagnosis of Heart Disease by the Heart Committee of the New York Tuberculosis and Health Association.

TABLE III. YEARS SINCE LAST ATTACK OF RHEUMATIC FEVER DURING FOLLOW-UP PERIOD

YEARS SINCE LAST ATTACK	PATIENT-YEARS OBSERVED			
	TOTAL	INACTIVE YEARS (NO.)	ACTIVE YEARS	
			NO.	% TOTAL PATIENT-YEARS
Over 1	13	10	3	23.0
2	31	26	5	16.1
3	36	32	4	11.1
4	40	37	3	7.5
5	30	29	1	3.3
6	13	13	—	—
7	11	11	—	—
Total	174	158	16	

TABLE IV. AGES DURING FOLLOW-UP PERIOD

AGES	PATIENT-YEARS OBSERVED			
	TOTAL	INACTIVE YEARS (NO.)	ACTIVE YEARS NO.	% TOTAL PATIENT-YEARS
9 through 13 years	46	30	7	15.2%
14 through 18 years	108	100	8	7.4%
19 through 22 years	20	19	1	5.0%
Total	174	158	16	

## DISCUSSION

The course in fifty-five rheumatic subjects who had remained free of rheumatic activity while taking prophylactic sulfanilamide for one to three years has been observed after this therapy was stopped throughout one to five years. Although the total data obtained in a group of this size are somewhat limited from a statistical point of view and would not justify drawing final or complete conclusions, the record of the follow-up period and the analysis of these data are sufficiently significant and of clinical interest to warrant presentation at this time.

The average recurrence rate in the 174 patient-years observed during the follow-up period was 9.7 per cent. Taking into account the rheumatic susceptibility factors represented in the group studied, this relatively low rate suggests that the period of inactivity and normal health maintained while taking prophylactic chemotherapy may have beneficially altered the rheumatic course. Considerably longer periods of follow-up in cases who have been treated, and comparison with matched cases who have never received treatment, will be essential to establish this point.

There was a lower recurrence rate in patients treated for two years (5.2 per cent) than for those treated for one year (9.1 per cent). These two groups were comparable in respect to rheumatic susceptibility and were followed throughout a coincidentally equal number of follow-up years. At first glance, the results in the group of eight patients that had been treated for three years is both startling and alarming unless analyzed in respect to the types of cases represented in that group. With one exception, because of past history of unusually frequent and severe attacks of rheumatic carditis, therapy had been extended deliberately in these cases. This factor of a higher susceptibility risk must be taken into account in the interpretation of the larger proportion of recurrences in this group. It is interesting and possibly significant, following the longer period of inactivity during three years of prophylactic treatment, that the subsequent recurrences should be distributed over later time intervals after stopping therapy than in the groups treated for shorter periods of time.

It has been frequently questioned whether there might not be danger of increased susceptibility to streptococcal infection and rheumatic recurrences on withdrawal of long-term sulfonamide prophylaxis. Evidence of such a proposed type of risk was not found in this particular group either by the general recurrence rate or by the fact that half of the recurrences did not develop until the second and third years after cessation of treatment.



The observed recurrences were analyzed in relation to those factors established as being effective in rheumatic susceptibility. The influences in the pattern of recurrences of age, type of past rheumatic history, and recency of activity continued to be evident during the follow-up period. The higher percentages of recurrences developed in the younger age-groups and in those who, prior to treatment, had had the more severe types of rheumatic episodes. With increasing time intervals since the last attack there was a progressive fall in the percentage incidence of active years in patient-years observed. Ninety-four per cent of the recurrences developed after the first year and within the fifth year of the last rheumatic episode.

To postulate an answer to the question as to how much benefit might have been obtained by further prophylactic treatment in this group had it not been terminated with observation of their subsequent course, an analysis was made of the results in prophylactic treatment years observed during the same period of time covered in the follow-up study. Possible effect from variation in the amount of rheumatic activity that occurs from year to year is thus eliminated in the comparison of time intervals concomitantly observed. Two reports have been made from the Bellevue Children's and Adolescents' Cardiac Clinics on the results in patients taking sulfanilamide (1939 to 1943, 181 patient-years) and sulfadiazine (1943 to 1945, eighty-seven patient-years) as a prophylactic measure. A further forty-five patient-years on sulfadiazine were observed from 1945 to 1946. Those years of treatment observed from 1941 to 1946 (the period of the follow-up study), and the group of patients then treated, were analyzed. It was found that the treated group was comparable to the follow-up group in rheumatic susceptibility in respect to past rheumatic history and recency of last attack, but that a higher proportion of the younger and presumably more susceptible ages were represented in the treatment years. There were four rheumatic recurrences during 233 patient-years of treatment, the average recurrence rate being 1.7 per cent. (In contrast there are the sixteen recurrences during 174 patient-years of follow-up with the average recurrence rate of 9.7 per cent.) It appears more than likely from the various observations given that further treatment would have been beneficial, particularly in those members of the follow-up group in whom younger age, recency of attack, and severe past rheumatic history represented a higher risk of recurrence.

Reports from a considerable number of clinics agree that sulfonamide has proved a valuable means of preventing rheumatic recurrences. The use of sulfonamide, however, is certainly not without possible dangers, and its prolonged administration requires more supervision and the maintenance of regular cooperation from the patient. Indiscriminate and indefinite use of such chemoprophylaxis in all rheumatic children and adolescents is both unwarranted and impractical either in clinic or private practice.

Decision as to which patients should best be protected by prophylactic treatment would appear to be based most wisely on an evaluation of the various recurrence risks in the individual case. Such factors as the following should be weighed: the higher risk of recurrences in the childhood and early

adolescent years, the fact that relapses appear most frequently in the years immediately following a rheumatic attack, and the higher incidence and greater danger of recurrences in those who previously suffered most frequent or severe attacks of rheumatic carditis. Where the risk is high for one or more of these reasons, it is suggested from observations made in this follow-up study that treatment be sufficiently prolonged to allow the opportunity for maintaining inactivity until adolescence has been reached or for a period of five years since the last attack in children or adolescents who have had repeated or severe episodes of rheumatic carditis.

#### SUMMARY

1. The course in fifty-five rheumatic subjects who had remained free of rheumatic activity while taking prophylactic sulfanilamide for one to three years has been observed after this therapy was stopped throughout one to five years, for a total of 174 patient-years.

2. The recurrence rate of active rheumatic fever was 9.7 per cent during the follow-up period. Patients who remained inactive and those who developed activity are analyzed in respect to length of treatment and data relevant to susceptibility factors.

3. In this group, there was no evidence of increased susceptibility to streptococcal infections and rheumatic activity at the time sulfanilamide was withdrawn.

4. Suggestions are made as to the types of patients probably best treated and the length of time treatment may be advisable in the various types.

Appreciation is expressed for the great help rendered by Miss Marie Summit, social worker for the Bellevue Children's and Adolescents' Clinics, whose untiring efforts made such a follow-up study possible.

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## SPOTTED FEVER TREATED WITH PARA-AMINOBENZOIC ACID

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FOR the past few years it has been known that the chemotherapeutic agent para-aminobenzoic acid effectively reduced the mortality from experimental murine typhus in white mice. This was proved by Snyder, and associates.<sup>1</sup> This agent has inhibited also the growth of epidemic and murine typhus rickettsias in the developing hen's egg, thereby prolonging the survival time of infected chick embryos, in the experiments of Hamilton and associates.<sup>2</sup> This experimental work indicated that para-aminobenzoic acid did not exercise a direct lethal action on the rickettsias, but in some way interfered with their growth and proliferation within tissue cells. It was thought that this action was due to a modification of enzymes as yet unidentified. Only the para form of this acid was effective.

Yoemans and associates<sup>3</sup> studied the therapeutic effect of this agent on human louse-borne typhus in Cairo, Egypt. Their results indicated that this disease was greatly modified, provided the drug was given early in the illness. Large doses, 24 to 28 Gm., were administered orally in twenty-four hours, and blood concentrations between 10 and 20 mg. were obtained. They experienced no toxic reaction other than temporary lowering of the white blood cell count in a few cases.

Appreciating the fact that para-aminobenzoic acid may be of value in other rickettsial diseases, Rose and associates<sup>4</sup> used it very effectively in one case of a white woman, aged 46, suffering with Rocky Mountain spotted fever. They administered 4 Gm. initially and then 2 Gm. in 25 c.c. of chilled 5 per cent sodium bicarbonate solution every two hours. The treatment was continued for four days with blood levels ranging from 6.6 to 18.6 mg. per cent. Their results were very gratifying in that the patient made a prompt and uneventful recovery. Following their suggested plan of treatment, a 4-year-old child infected with spotted fever was effectively treated in Grandview Hospital, Sellersville, Pa.

### CASE REPORT

L. B., a white female child 4 years of age, was admitted to Grandview Hospital July 17, 1946, complaining of fever, chills, vague pain in joints, and sore throat. On admission, her temperature was 101.2° F., pulse 130, and respiration 30. July 10, 1946, one week before admission to the hospital, the child developed a mild sore throat followed by fever and intermittent pains in various joints of her body. She continued to have daily elevations in temperature, and on July 15 a papular rash developed on the thorax. On this same day the child began to complain of abdominal pain, and a soft systolic murmur was heard at the apex. The attending physician suspected rheumatic fever and for such she was treated. When she failed to respond to salicylate therapy and bed rest, she was admitted to Grandview Hospital, where a tentative diagnosis of spotted fever was made. The mother was again carefully interrogated and related that on June 30, 1946, she had taken the child on a picnic. Upon returning home she removed a tick from the child's underwear. It was

not attached to the skin nor could she find any evidence of a bite. Unfortunately, she did not give this history to the attending physician on previous questioning, as she had considered it of no importance.

Physical examination revealed a thin, pallid, female child, manifesting evidence of toxicity and drowsiness. The skin was covered with a generalized papular rash and small petechial spots were visible on the hands. There was generalized adenopathy. The pharynx was slightly injected. There were no abnormal findings in the lungs. The heart was rapid but not enlarged and a soft grade 2 systolic murmur was heard at the apex. The liver was tender and enlarged two fingerbreadths below the costal margin. No other abdominal organs were palpable. The extremities were negative except for the papular rash. All reflexes were normal. Examination of the eye grounds revealed no abnormal findings. The laboratory findings during her stay in the hospital are given in Chart II.

CHART I. TEMPERATURE

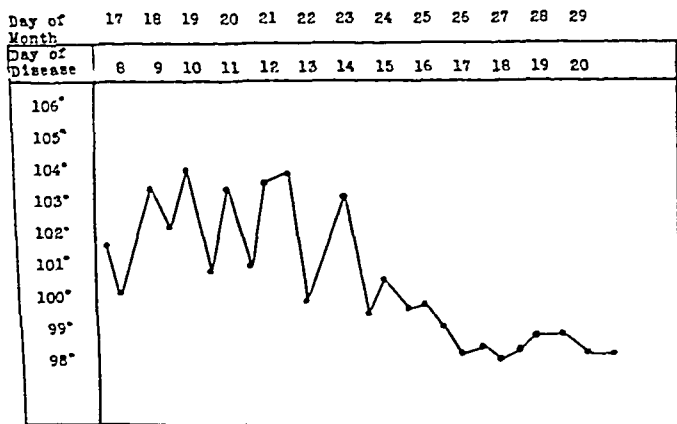


CHART II. LABORATORY FINDINGS\*

DATE	URINE	PAB† BLOOD LEVELS	AGGLUTINATION AND OTHER TESTS, ETC.	BLOOD STUDIES
7/17	2 albumin; hyaline and granular casts 30-35/lpf; W.B.C., 2-3/hpf		Typhoid O, negative Typhoid H, negative Paratyphoid A, negative Paratyphoid B, negative <i>B. Abortus</i> negative Proteus OX-19, positive 1:40	Hb., 11.5 Gm. %; R.B.C. 3,960,000; W.B.C. 7,900, polymorphonuclears, 57%, monocytes, 2%, lymphocytes, 41%; sedimentation rate, 19 mm. in 60 min.
7/18				Blood culture taken
7/20	2 albumin; hyaline and granular casts occasional; W.B.C., 6-8/hpf; R.B.C. oc- casional			Blood culture negative
7/22		8.8 mg. %	Proteus OX-19, positive 1:640	W.B.C. 12,700; blood culture negative
7/23		None pres- ent	Heterophile antibody reaction negative	W.B.C. 12,500; blood culture negative
7/25	W.B.C., 3-4/hpf	6 mg. %	Proteus OX-19, positive 1:640	W.B.C. 8,100 Blood culture negative

\*On July 24, serum from the patient was sent to Dr. Charles Armstrong, Division of Infectious Disease, U. S. Public Health Service, Bethesda, Maryland. The following results were reported: complement fixation tests: endemic typhus, negative; Rocky Mountain spotted fever, positive 1:512, agglutination test: *B. proteus* OX-19, positive 1:1280.

†PAB para-aminobenzoic acid.

*Treatment.*—As soon as a positive diagnosis of Rocky Mountain spotted fever was established, para-aminobenzoic acid was administered, the initial dose being 4 Gm. followed by  $\frac{1}{2}$  Gm. every hour with 5 c.c. of 5 per cent solution of sodium bicarbonate. There was no nausea. The frequency of administration was deemed necessary because of the rapid elimination of this drug. We encountered great difficulty in obtaining an adequate supply of the acid, and on July 23 none was available. It was on this day that her blood concentration was zero and her temperature rose to 103° F. Late in the evening of July 23, more of the drug was procured and another initial dose of 4 Gm. was given. For the following two days she again was given  $\frac{1}{2}$  Gm. every hour. The drug was discontinued on July 25. A total of 30 Gm. had been administered.

Within twenty-four hours after the drug was started, the child showed remarkable improvement; she became more alert and talkative, ate well without help, and sat up in bed playing with her toys. The omission of the drug on July 23 did not seem to have any unfavorable effect except for the rise in temperature. After that date her temperature returned to normal and her condition improved rapidly. Recovery was uneventful and she was discharged from the hospital on July 29. By this time the rash had completely disappeared and only small discolored areas remained.

#### COMMENT

As confirmed by laboratory tests, history of a tick bite, and typical clinical manifestations, this child undoubtedly suffered from Rocky Mountain spotted fever. Para-aminobenzoic acid effectively produced a decrease in temperature and rapid improvement in the child's well-being. It is to be noted that the high blood concentration as suggested by Rose and associates<sup>4</sup> was never obtained, but in spite of this the clinical course, after administration of the drug, was one of prompt recovery.

It is interesting to note the case in which the early stages of this disease might be confused with rheumatic fever. This child had many of the typical symptoms of rheumatic fever in the early days of her disease, sore throat, joint pains, abdominal pain, and a heart murmur. Since some cases of rheumatic fever develop a skin rash, this finding would only add to the confusion. The fact that the history of exposure to a tick was not obtained from the mother at the onset of the disease merely emphasizes the extreme importance of a careful history. It was not until this clue was uncovered that a final diagnosis was definitely established.

An unusual feature in this patient was the atypical distribution of the rash, which in the early stages of the disease was first found on the thorax and then spread to the extremities. In spotted fever the rash usually occurs first on the extremities and later spreads to the rest of the body.

Bucks County, Penn., is heavily infested with *Dermacentor variabilis* ticks. During the tick season many people in this county are bitten, but the patient reported is the first one to develop spotted fever in the northern part of the county within the last three years.

#### SUMMARY

Rocky Mountain spotted fever in a 4-year-old child was effectively treated with para-aminobenzoic acid. It is hoped that the drug will be used more frequently in the treatment of this dread malady, and the results promptly reported.

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## POSTSCARLATINAL GANGRENE WITH PROLONGED PROTHROMBIN TIME

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A RARE complication of scarlet fever is gangrene of the extremities associated with extensive hemorrhages; in 37,000 cases of scarlet fever at Municipal Contagious Disease Hospital before 1934, Dick and associates<sup>2</sup> observed one patient with gangrene, and found only fifteen previously reported cases. Since then Cust,<sup>1</sup> Hoyne and Smollar<sup>3</sup> (who surveyed 30,000 cases of scarlet fever) Lagréze,<sup>4</sup> and Stupenengo<sup>7</sup> have each added one case to the literature. In addition, a similar type of gangrene has been reported following chickenpox.<sup>6, 8</sup>

The clinical picture is that of an extensive fulminating gangrene, usually beginning from nine to twenty-three days after the onset of scarlet fever, from which an apparently uneventful recovery has been made. In at least nine of the twenty cases, the gangrene has been severe enough to require amputation of one or both lower extremities. The distribution tends to be symmetrical, most often occurring over the malleoli, knees, and iliac crests. The sharp line of demarcation of the gangrenous areas is striking. In only one case<sup>2</sup> has internal bleeding been noted. There is a remarkable lack of toxic signs, blood cultures when taken have been negative,<sup>1, 2, 4</sup> and normal blood pressure has accompanied the acute process.<sup>1</sup> The period of active bleeding has been limited to several days,<sup>3</sup> and once the bleeding has stopped there have been no exacerbations.

Hematological studies are incomplete in most of the reported cases. However, Dick's patient<sup>2</sup> had 150,000 platelets, bleeding time 5 minutes, and clotting time 5½ minutes; while Cust's patient<sup>1</sup> had 36,000 platelets, bleeding time 7 minutes, and a negative Rumpel-Leede test; and Lagréze's<sup>4</sup> had 164,000 platelets, bleeding time 2 minutes, and clotting time 8½ minutes with a positive Rumpel-Leede test. No prothrombin estimations are reported in the literature.

The pathologic findings are variable. Four of the fifteen cases reviewed by Dick and associates<sup>2</sup> showed patients with thromboses in the amputated limbs, but their own patient showed only recent thrombophlebitis without thrombi. No arterial emboli were found in the amputated limbs of Cust's patient,<sup>1</sup> while microscopic sections of the muscles just above the gangrene in Hoyne's patient<sup>3</sup> revealed acute myositis associated with panarteritis of most of the arterioles and no change in the venules.

The following is the only one out of sixty-five patients with scarlet fever at Duke Hospital to show gangrene. It is presented because of the striking abnormality of the blood clotting mechanism.

## CASE REPORT

C. F., a 23-month-old white girl, was admitted to Duke Hospital Jan. 6, 1916, because of ecchymoses over the extremities of twenty-eight hours' duration.

*History.*—The patient has seven normal, older siblings and one brother who died in infancy of pyloric stenosis. Her mother has urticaria and a paternal aunt has asthma, but there are no blood dyscrasias or hemorrhagic diseases in the family. The child had always been a feeding problem, and refused all food except cow's milk, potatoes, cereals, and an occasional orange. She had never had any allergic or hemorrhagic manifestations, and no contagious diseases until the present illness. Tuberculin test six months before admission was negative. During the month prior to admission she had had no contact with poisons or medication of any kind except paregoric, aromatic spirits of ammonia, elixir of malt-pepsin, Upjohn's Vitakon and boric acid-glycerin ointment for the skin.

*Present Illness.*—Three weeks before admission the child had a febrile illness with an erythematous rash, followed by desquamation which was marked over the palms and soles. As the rash faded there was a vesicular eruption around the lips, but for one week before admission she apparently was well. Another child in the family had a similar rash ten to fourteen days before the patient. Twenty-eight hours before admission, the patient complained of pain in the right leg, and a red macule about 2 cm. in diameter was noted above the lateral malleolus of the right ankle. Within two hours, petechiae and ecchymoses covered the leg and buttock and a similar process was beginning on the other leg. Hot compresses were applied and the child was put to bed where she was playful but refused all food except milk. Eight hours before admission, a purple area started on the right shoulder and spread rapidly.

*Physical Examination.*—Temperature was 38.3° C. (101° F.); pulse, 130; and blood pressure, 108/68. The patient was a well-developed, well-nourished, 23-month-old female child standing in bed and using all extremities well except the right arm, on which there was an extensive, well-demarcated, purple ecchymosis extending from the shoulder to the elbow. There were scattered petechiae over the remainder of the arm and hand; the arm was moderately swollen and the hand slightly so; the radial pulse was good, although the upper arm and shoulder were cold. The skin over the knees had a bluish tinge from innumerable petechiae; small ecchymotic areas were beginning on the buttocks; petechiae were thinly scattered over the remainder of the legs, thighs, buttocks, and the right side of the trunk anteriorly; the remainder of the skin and mucous membranes were very pale without petechiae or jaundice; and the posterior tibials and dorsalis pedis pulses were strong bilaterally. The upper respiratory tract was not remarkable. Examination of the heart showed the point of maximal impulse just beyond the nipple line, regular rhythm, rapid rate, and sounds of good quality without murmurs; the lungs were clear; the spleen was barely palpable at the costal margin; the liver was not palpable; there was no abdominal tenderness; and there was no evidence of bleeding from any of the body orifices.

*Course in the Hospital.*—

*First Hospital Day:* After admission at 10:30 P.M. the ecchymotic areas continued to enlarge, but the patient did not appear toxic. Laboratory findings were: Hemoglobin, 7.0 Gm. per 100 c.c.; red blood cells, 3,310,000; hematocrit, 21.8 (cor.); white blood cells, 32,170, with 79 per cent polymorphonuclears, 11 per cent juveniles, 2 per cent myelocytes, and 8 per cent small lymphocytes. Platelet count was 100,000, and platelets appeared normal on the stained smear. Tourniquet test was negative. The red cells settled rapidly to the bottom of the Wassermann tube, and in eight hours there was no evidence of a clot in the red cell layer or the supernatant plasma. Kahn, Kline, and Mazzini tests were negative, and blood cultures were sterile. Stool showed no gross or microscopic blood.

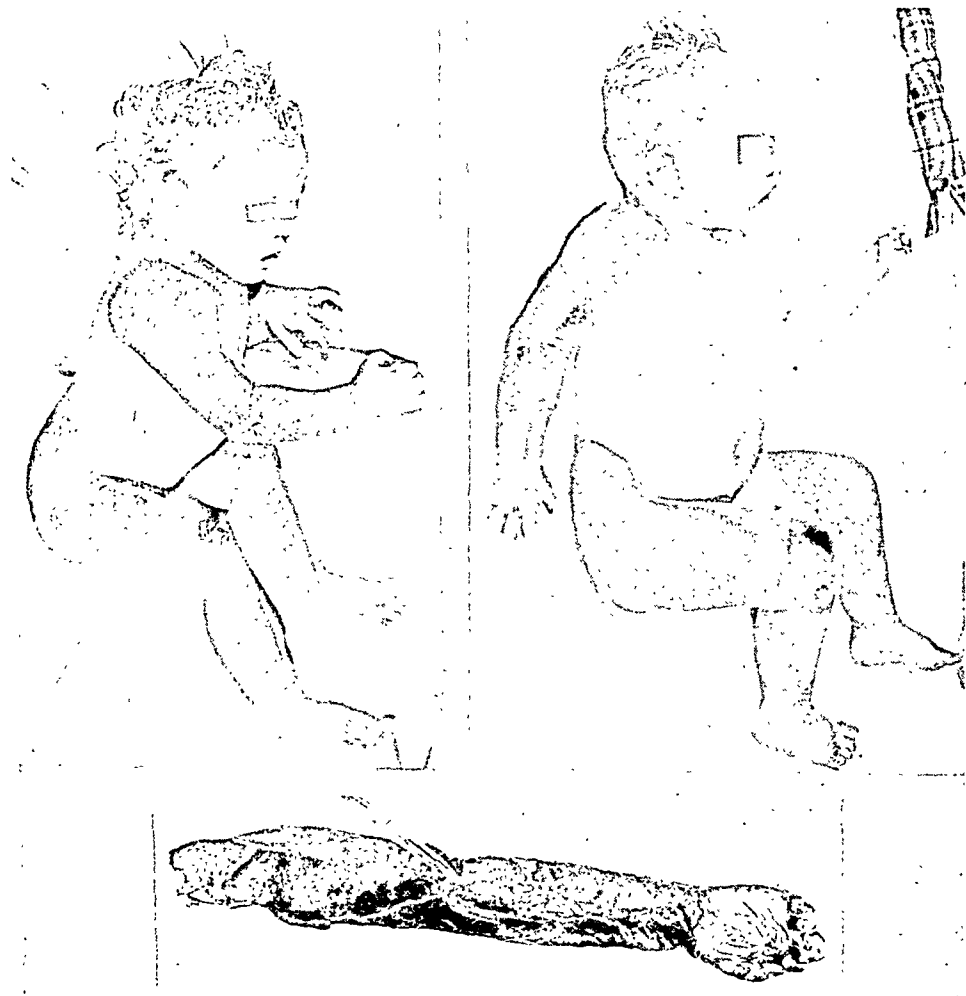
*Second Hospital Day:* At about 2:00 A.M., the patient was standing in her bed crying for water when she vomited clear watery material and suddenly became semicomatose, though her blood pressure remained 108/68. Transfusions were started immediately, and she received 500 c.c. of bank blood within the next twenty-four hours as well as penicillin and Vitamin



K, and the extremities were loosely wrapped in sterile cotton. Despite this the ecchymoses continued to enlarge and by afternoon she appeared as in Fig. 1, *A*. Clotting time by Lee-White's macro method showed the blood to remain fluid after forty-eight hours, except for a tiny clot that appeared in about two hours. By the capillary tube method the clotting time was 16 minutes: the bleeding time (Duke's method) was 8 minutes. The prothrombin

A.

B.



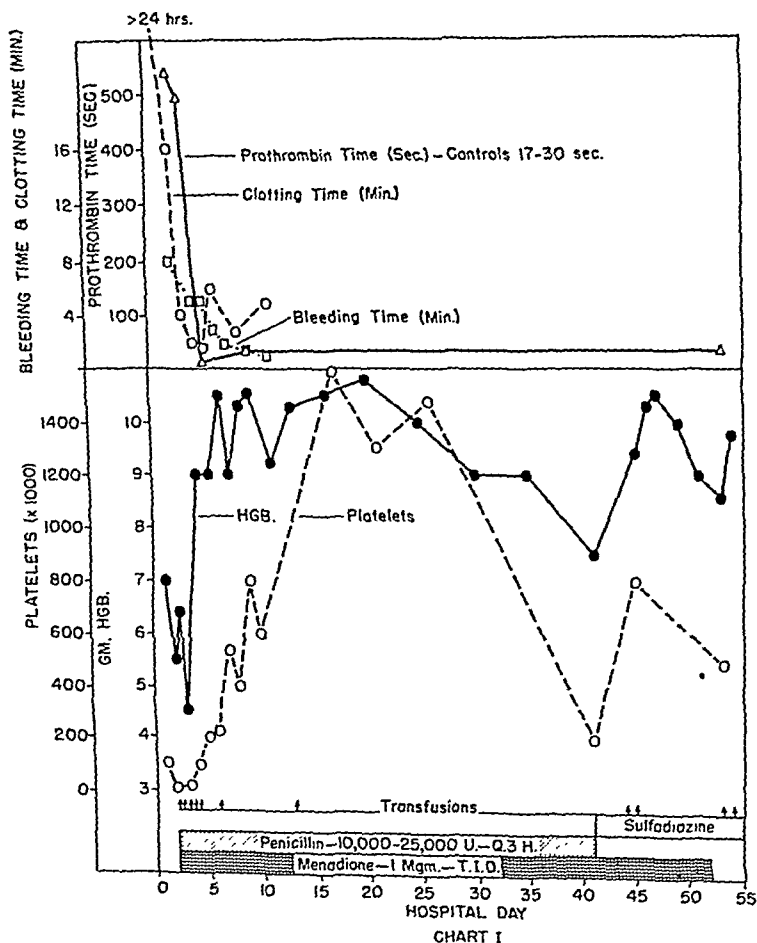
C.

Fig. 1.—*A*, appearance of the child on the second hospital day. *B*, appearance of the child after the cessation of bleeding (fourth hospital day). *C*, the disarticulated right arm. The slough of the upper arm included only skin and subcutaneous fat.

times (Quick's simple clinical method) were 8 minutes, 56 seconds, checked at 9 minutes, 10 seconds (control, 17 seconds), and 8 minutes, 8 seconds (control, 21 seconds). Tourniquet test (Rumpel-Leede) was again negative. Platelets at this time, however, were less than 1,000 per cubic millimeter\* and were very rare on the stained blood film.

\*Platelet counts were done on a fresh supravital preparation by comparing the number of platelets to the number of red blood cells.

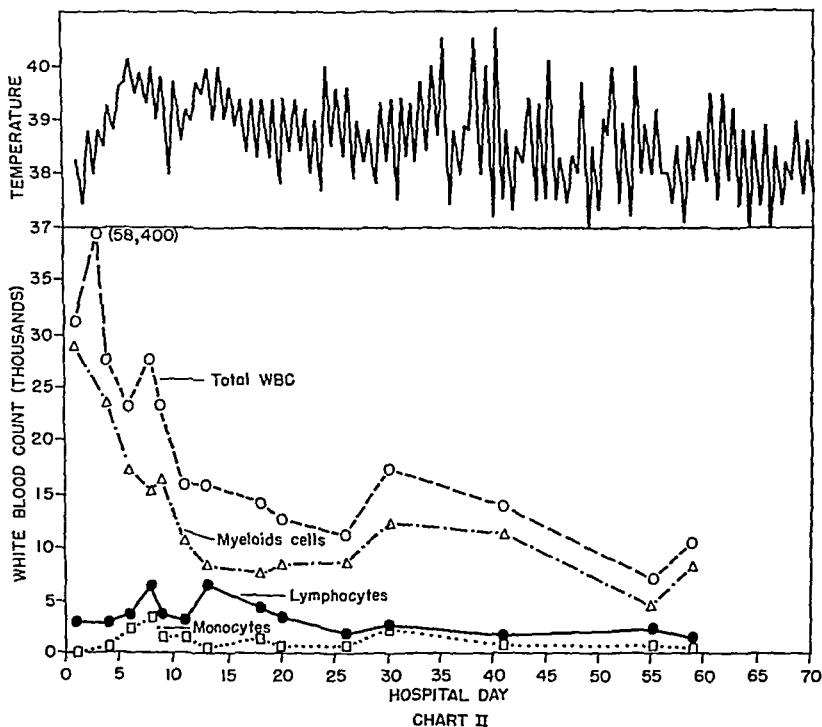
*Third Hospital Day:* In the morning the areas of gangrene were still spreading, and a pinkish halo was appearing around the margins (Fig. 1, B). The right radial pulse was no longer palpable though the dorsalis pedis pulses were good bilaterally. The spleen was now palpable about 2 cm. below the costal margin as was the liver, and the child had a slight nosebleed. The hemoglobin had dropped to 4.5 Gm., platelets were 25,000, and white blood cells were 58,400. For the only time throughout her course there was microscopic blood in the stool though none in the urine. About noon the child suddenly became cold, clammy, and unresponsive. Banked blood was given immediately by the pressure method followed by a continuous intravenous infusion of saline, dextrose with accessory vitamins, and freshly drawn, citrated blood. By 2:00 P.M. the ecchymotic areas had stopped spreading, and the child's color became good (Fig. 1, B).



*Subsequent Course:* By the fifth hospital day the blood findings approached normal: Hemoglobin, 9 Gm.; red blood cells, 3,900,000; platelets, 200,000 with a prothrombin time of 15 seconds (control, 22 seconds), bleeding time, 5 minutes, and clotting time, 2½ minutes (capillary method). From this time on, the blood findings were not remarkable except for a platelet rise to 1,600,000 on the seventeenth hospital day (Charts I and II). On the eighteenth hospital day the fibrinogen was 0.57 Gm. and later fell to 0.43 Gm. per 100 c.c. plasma.

After the bleeding stopped, the hemorrhagic areas rapidly became definitely gangrenous. The limbs were kept in loose bandages of sterile cotton as long as the tissues appeared

viable, but on the eleventh hospital day dry rayon dressings covered with pressure bandages were begun. On the fifteenth day the arm spontaneously disarticulated at the elbow, slough developed over the buttocks and knees, and self-amputation of the toes began. The course was complicated by a mild pyelitis, a pyocyanus infection of the denuded areas, and a stubborn miliaria-like rash of the skin which made grafting impossible. The patient was discharged against advice seven months after admission. At this time the humeral stump as well as the other areas had granulated well but still had not epithelialized completely, and there was some contracture of both knee joints. Local treatment consisted of débridement, saline baths, pressure bandages, and physiotherapy. The temperature curve (Chart II) was of a septic type with short periods of almost normal temperature during the last four months of her hospital stay. There was no further bleeding tendency.



#### DISCUSSION

In the previously reported cases the emphasis has been on the gangrene<sup>1-3</sup> and the blood picture has not been extensively studied; however, in our case we had the opportunity of watching the gangrene develop and of following the blood picture during the development and recession of the gangrenous process. When the patient was first seen, the picture was that of a fulminating purpura, yet the platelets were 100,000, and appeared adequate on the stained smear. Clinically, then, the period of most active bleeding preceded the platelet fall; furthermore, the tourniquet test was negative. The most unusual feature of this case was the prolonged prothrombin time done by Quick's bedside method<sup>5</sup> in which care was taken to add the full amount of thromboplastin. It is not known whether the prolongation of the clotting in this test is due to

deficiency in prothrombin alone or whether an excess of heparin or diminished fibrinogen played a role. It was impossible to secure sufficient blood for testing these at the time of active bleeding.

The very high leucocyte count which reached its maximum at the height of the bleeding is also interesting, as is the actual and relative increase in mononuclear cells and platelets with high fibrinogen during the active period of slough (Chart II). The disarticulated arm (Fig. 1, C) showed only necrotic tissue.

#### SUMMARY

1. A review of the literature of postscarlatinal gangrene reveals twenty cases.

2. A new case of postscarlatinal gangrene with thrombocytopenia and prolonged prothrombin time is presented with the laboratory findings.

The authors wish to thank Dr. Jerome S. Harris for his helpful suggestions in the preparation of this article for publication.

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## EXPERIENCES WITH JAPANESE PEDIATRICS

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IT IS now generally recognized that the American occupation of Japan is proceeding with remarkable smoothness. On all sides American troops are mingling freely with the Japanese population. It is not the purpose of this account to discuss at length Japanese psychology or to attempt to speculate on the proportions of purely external politeness and of heartfelt friendliness which are making up the warm reception being accorded the occupation forces. As a member of the Army Medical Corps, I was able to utilize a recent five- and one-half-month stay to advantage by studying Japanese medicine and pediatrics. Returning well stocked with reprints and personal communications, I feel that the facts to be presented are reasonably accurate.

At this point, a brief description of the development of Japanese medicine seems in order. Japanese medicine became oriented along western lines after the opening of the country to outside influences about a century ago through the efforts of Commodore Perry. Actually, it was well toward the end of the nineteenth century before much progress was made. This coincided with the Golden Era of German medicine. For this reason, Japan came overwhelmingly under the influence of the leaders of medicine in Germany and Austria. With some exceptions, this condition held until the present war. As a result, German texts and publications were widely read, and large numbers of promising workers were sent to the clinics of Germany and Austria. On returning to their homeland, these men labored to set up replicas of the establishments where they had studied, and German became the scientific language of the medical profession. Up until the present time, clinical records, writings, and dissertations are literally seeded with German terms and phrases; this applies to diagnostic terms in particular.

Following German lines, faculties were set up, with "professors" ruling the clinics in rather autocratic fashion. A sharp cleavage between the full-time teacher and the practicing physician was established. The latter have had virtually no access to public or teaching hospitals. This appears to have brought about an ultrascientific, impersonal attitude on the part of the teacher, while the practitioner, on the other hand, frequently sets up a small private hospital, usually poorly equipped, and regards medicine largely from a commercial standpoint. The oriental tendency to contemplate suffering with more indifference than we do, the great density of population, and the caste system (the physician and especially the "professor" naturally falling into an upper bracket) serve to accentuate the situation.

During the war, the Government made terrific demands on the medical profession. The "home front" was greatly depleted, supplies were scarce, and

buildings were allowed to deteriorate unbelievably. It would almost seem as though the Japanese have better luck in maintaining their flimsy, native structures than the Western style buildings. It was interesting to hear that few of the senior members of the medical faculties were called to military service. A personal opinion expressed by one eminent teacher was that "perhaps the military surgeons feared the competition of men from teaching centers."

Medical education in Japan has lacked uniformity. The standards of the medical faculties of the seven Imperial Universities (nine in pre-V-J days) are the highest. In addition, there are about seven government schools of university rank. These also have fairly high standards. Three private medical schools, all situated in Tokyo, are of university rank and have good reputations.

In Japan there are also medical professional schools of lower rank. In prewar days, there were six of these for men and three for women. Women cannot attend the other institutions except for work on a graduate level. During the war, countless emergency courses and further medical professional schools were opened. As a result, one would assume the presence of a large number of poorly trained graduates. The good schools require a premedical course, extending about the same number of years as our own. The medical professional schools have combined premedical and medical courses lasting between four and five years in ordinary times.

Internships as we know them are not generally available. A clerkship is served during the medical course. Further practical experience in clinics is gained by assistantships which are always along specialized lines. Medicine is a very popular profession and the students are selected from a large field of applicants on a competitive basis. "Weeding-out" examinations are given on several occasions. The tuition, especially in the government schools, is relatively low.

Along the lines of modern equipment Japanese medicine is far inferior to our own. Much of the apparatus is old. Central supply rooms are not generally known. At medical centers each specialty usually maintains its own buildings and tends to function independently of the others. The resources of Japan are meager. Furthermore, most of the substance of the country has been depleted by war for some years. At the present time, all medical leaders are keenly aware of the strides made by American medicine and also of their own backwardness. They are anxious to acquire knowledge coming from our shores.

With this background, the reader will, perhaps, understand better the personal pediatric experiences to follow.

Being stationed near the Kyushu Imperial University, I had excellent opportunity to become acquainted with Japanese pediatrics. This school was regarded as having one of the best faculties in the country. The medical school and hospital was a large plant consisting of about twenty buildings. The total bed capacity was said to be about 1,000. Externally, some of the buildings were quite modern and even impressive. However, most of them were in need of considerable repair. The prewar enrollment was about 565 students in the medical course.

The pediatric clinic was housed in an old, two-story structure of frame and plaster with a bed capacity of sixty. A laboratory, formula room, classroom, library, and faculty office comprised the remainder of the structure. Private rooms were available. In Japan, members of the family always stay with the patient; they frequently cook for him and even nurse him. This complicates the picture, especially in the wards.

The library was fairly complete and up to date until the time of Pearl Harbor, and leading pediatric journals of American and German origin were available.

The staff consisted of a professor and an assistant professor. There were a number of instructors and about twenty assistants. These served for an average of three years, thus obtaining pediatric training.

My first visit to the Children's Clinic was unexpected and unannounced. However, I was immediately ushered into the presence of Professor Munenori Enjoji, the head of the pediatric department. I was received with all the usual politeness of the Japanese. After some minutes of conversation in English which progressed fairly well, we discovered that German was an even better tongue in which to converse. It was soon brought out that his training had been in the United States, Germany, and Austria. Upon returning to Japan in the early days of the war, he became the third incumbent of the Chair of Pediatrics of the Kyushu Imperial University, which position he still holds.

Professor Enjoji and I became well acquainted and met weekly for the discussion of pediatric problems and the interchange of ideas. From him I obtained a brief history of Japanese pediatrics.

In 1888, Hirota, a pupil of Kohts, then Professor of Pediatrics at Strassbourg, became director of the Children's Clinic at the Imperial University in Tokyo. In 1895, Ito, a student of Heubner in Berlin, became head of the Children's Clinic at the prefectural hospital in Fukuoka. From this developed the Kyushu Imperial University. In 1903, Hirai, who had studied under Czerny in Breslau, became the head of the pediatric department at the Imperial University in Kyoto. These men then became the early leaders of Japanese pediatrics.

At the Kyushu Imperial University, Ito was succeeded by Mita, who in recent years became emeritus professor, to be succeeded by Enjoji. It is interesting to note that the history of Japanese pediatrics is not much shorter than that of pediatrics in this country.

In prewar days, there were 3,000 pediatricians in Japan, out of a total of 65,000 licensed physicians. It is not possible to state whether these were exclusive specialists, since there are no specialty boards in Japan. Pediatricians are usually located in the larger centers.

Professor Enjoji and his co-workers read avidly any journals I was able to lend them. Recent American pediatric texts were literally devoured. Enjoji impressed me as alert and well trained. His clinic, while old and in poor repair, was clean and orderly. He appeared to be deeply interested in pediatrics and was well aware of the shortcomings of Japanese pediatrics. He repeatedly

stressed to me the need for much more emphasis on preventive pediatrics and on growth supervision than was being made in Japan.

Generally, the pediatric facilities are represented by the children's clinics of the various medical faculties, children's departments in prefectural hospitals, and by the work of the private pediatricians. The last group frequently maintain their own small private hospitals. Red Cross hospitals and hospitals supported by various Christian missionary groups are usually of a model type in respect to the buildings, their maintenance, and the medical care given. St. Luke's Hospital in Tokyo, the International Red Cross Hospital in Kyoto, and the Hospital of Our Lady in Tokyo are notable examples.

On the other hand, the communicable disease hospitals do not appear to be well run. They have the atmosphere of a "pest-house," offering for the most part, only a segregated environment, and providing little active treatment.

It must be emphasized that systematic pediatric supervision and the use of routine immunization are very rare practices in Japan. The exception to the latter would be smallpox vaccination which is done fairly universally since it has been decreed compulsory, the regulations requiring one vaccination within six months after birth and another in the tenth year of life. However, occasional lapses occur, and smallpox is not unknown in Japan. In fact, during the past year there has been a considerable number of outbreaks which no doubt, are related in part to the general disintegration of the war and its consequences. Some diphtheria immunization is done, as there is considerable diphtheria in Japan.

The teaching of pediatrics is carried out with much emphasis on didactic methods. In proportion to the large student bodies the number of both inpatients and outpatients available for teaching is not very large. At present, much thought is being given to the revision of the curriculum along American lines. There is much discussion given to the introduction of democratic methods in the conduct of the entire medical faculty setup. I was frequently asked how professors were appointed in the United States and especially how they were disposed of if unpopular or unsatisfactory.

There appeared to be an abundance of assistants at the various children's clinics. These are the equivalent of our pediatric residents and fellows. They seemed very eager to learn in the usual fashion of the Japanese, with notebooks, pencils, and pens always in evidence.

Judged by our standards, most of the equipment is quite meager in the average children's clinic. This is especially true in regard to facilities for parenteral therapy. Rubber is very scarce, hence much of the tubing is in poor condition. Blood transfusions are usually given with 50 c.c. or 100 c.c. syringes; the total quantity is small according to our standards. In general, one can safely say that equipment is twenty to thirty years behind our own.

Therapy is conducted along lines similar to ours. Penicillin is now becoming available; sulfapyridine and sulfaguanidine are the chief sulfonamides; sulfathiazole and sulfadiazine are little known. Biologicals are quite scarce. Diphtheria antitoxin is available, but only in small quantities. One cannot escape the impression that while therapy is important, immediate results are not



as paramount as with us. In the university clinic the patient is distinctly subservient to the physician. One sees many patented, "coal tar" products in pharmacies. Again this seems to indicate the German influence.

Medical libraries appear to play an important part in medical education. However, since Pearl Harbor they have stagnated. Textbooks are almost impossible to obtain and most students must study from notes.

Research seems to be stressed a good bit. In fact, one receives the impression at times that it is forced like a hothouse plant. At the present time the work in pediatrics is largely clinical research. Formerly, much attention was given at the Kyushu Children's Clinic to the bacteriology of the dysenteries.

From an economic standpoint, the medical teacher is poorly paid at present. His salary is fixed and has not kept pace with the inflationary price rise. He has no opportunity for adding to his income from private practice or even consulting work. He seldom owns an automobile. Nevertheless, his prestige is still great.

The physician in private practice has somewhat better opportunities for making a living. Compulsory health insurance exists for certain classes of workers, and there are many voluntary health insurance societies. However, fundamentally, private practice is conducted independently by the physician. As previously stated, many operate small hospitals of their own, but these, as a rule, are poorly equipped. One of the leading pediatricians in Fukuoka goes about on a bicycle. House calls are less frequently made than in the United States. Since telephones are scarce, this instrument plays a less important part than it does in American medicine.

#### SPECIFIC PEDIATRIC PROBLEMS

The high birth rate of the Japanese is well known. Most families have at least six children; in fact, to have less is almost not respectable. While some of this is due to the expansionistic policy, one does gain the impression that children are genuinely liked for their own sakes. Boys are more welcome than girls. Giving birth and rearing children are regarded as natural functions. A midwife usually attends the delivery, which characteristically takes place at home; hospitals and obstetricians are largely reserved for pathologic cases and wealthy persons.

*Growth and Development.*—The average birth weight of a full-term, male infant is approximately 6 pounds, 11 ounces (3.06 kg.), and of a full-term, female infant, 6 pounds, 8 ounces (2.95 kg.). This is, of course, less than the figure for the United States. The length is 49.4 cm. for boys and 48.5 cm. for girls, which is lower than the American figures of 50.4 cm. and 49.7 cm., respectively.

At 16, the Japanese boy's height averages 147.7 cm. and the girl's, 144.1 cm., in contrast to the figures of 171 and 167 cm. for American boys and girls, respectively.

The weight of boys at 6 years is 17 kg., at 12 years, 30 kg., and at 16 years, 40 kg. American weights average 20.4, 39, and 61 kg., respectively, for the same age groups.

Japanese girls weigh an average of 16.5 kg. at 6 years, 30 kg. at 12 years and 40.4 kg. at 16 years. Average American weights are 19, 39, and 56 kg. for the same age groups.

From tables made available to me I would conclude that motor development and mental development in Japanese children are comparable with our own children.

*Problems of Infancy.*—Breast feeding is taken for granted in Japan. In fact, the big problem is to educate mothers to discontinue nursing their infants at a reasonable time. "Late weaning disease" is an entity under much discussion. In previous times beri-beri was a problem of greater extent than recently.

Anemia, poor muscle tone, and rachitic changes are all described as the fate of a late-weaned infant. Many children are not weaned until well into the second year. During this period of protracted nursing virtually no other nourishment is given. It would appear that this factor is responsible for the above manifestations.

Under the influence of pediatric clinics some progress is being made toward weaning at one year. When a breast milk substitute is needed, quite a problem is faced. Animal milk is very scarce. Cow's milk can be obtained in small quantities. Thin rice gruel is the usual substitute for milk; obviously, it is far from satisfactory. Soybean milk has become quite popular and the results with its use are quite good. A synthetic "milk" made up from peptonized sardines, millet jelly, cod liver oil, sesame oil, and garden radishes has been used to some extent, and the results were fairly satisfactory.

*Dysentery and Dysentery-like Diseases.*—These have always offered a considerable problem in Japan. The universal use of "night-soil" for fertilizer, the abundance of flies, the predominant use of "privies" rather than flush toilets, all contribute to this group of diseases. A good deal has been done on the bacteriology of these cases by the Japanese. Mita, the Emeritus Professor of Pediatrics, is credited with considerable work, especially with isolating a group of paradysentery organisms.

Therapeutically, sulfaguanidine or sulfapyridine, diet, and fluid balance comprise the therapy. It is claimed that sulfapyridine is more effective than sulfaguanidine. Rice gruel is used largely as the first form of nourishment in these cases.

During the past twenty-eight years, Mita has studied 2,676 patients with dysentery. Of this group, causative organisms in 1,750 patients were isolated.

An interesting entity described in Japan is "ekiri." This is seen not only in cases of acute colitis, but also in some cases of high fever in association with many infections. Symptoms are sudden onset, vomiting, stupor, delirium, convulsions, and coma. The susceptible age is generally from 2 to 6 years. While many theories have been advanced in regard to etiology, an abnormal stimulation (spasm) of blood vessels and of the autonomic nervous system as a whole, coupled perhaps with an "ekiri diathesis" is set up as an explanation.

The etiology and nature of "ekiri" appear somewhat obscure. One wonders whether it merely represents a terminal picture of an overwhelming infection. The Japanese, endorsing the idea of spasm, have employed atropine and claim some successful results. A sharp reduction in mortality has been reported.

*Tuberculosis.*—Tuberculosis is without doubt the biggest public health problem in Japan. Tuberculous meningitis is a very frequent form in infancy and early childhood. In 393 patients studied, 17.74 per cent were in infancy and 64.5 per cent in early childhood.

The mortality from all forms of tuberculosis in children under one year of age was 75 per cent, from 2 to 5 years inclusive it was 38 per cent, and from 6 to 11 years inclusive, 14.4 per cent. During puberty the death rate increased to 28.26 per cent.

The percentage of positive tuberculin reactions among school children in Fukuoka ran as follows:

First Grade—12.8 per cent positive reaction

Second Grade—17.5 per cent positive reaction

Third Grade—21.7 per cent positive reaction

Fourth Grade—25.5 per cent positive reaction

Fifth Grade—27.4 per cent positive reaction

Sixth Grade—31.2 per cent positive reaction

Tuberculosis is the leading cause of death in Japan. In 1938 the death rate for the entire population was 206 per 100,000. As a comparison, during the same year in the United States registration area, the death rate was 49 per 100,000.

*Atomic Bomb Disease.*—A small group of children (twenty) exposed at Hiroshima and Nagasaki were studied and reported. These were children who had survived the initial damage. Symptoms consisted of depilation, diarrhea, hemorrhage into the skin, sore throat, gingival hemorrhage, and ulceration of the mouth. All of this group had some leucopenia and anemia. Bone marrow studies revealed an increase in the young forms of granulocytes (40 to 60 per cent). It was concluded that children subjected to heavy irradiation died shortly after the bombing. The children who survived appeared to recover more satisfactorily than corresponding cases among adults. It was felt that blood regeneration was more active in children. Four of the twenty died. Diarrhea was marked in one patient, petechial hemorrhages in another. Ulceration of the oral cavity and convulsions were the most striking symptoms in two.

*Intestinal Parasites.*—Due to the widespread habit of fertilizing with "night-soil," parasitic infections are quite abundant. Flush toilets are quite rare, except in modern buildings. A survey of 581,809 persons in 1937 revealed 48 per cent carrying parasite eggs. *Ascaris lumbricoides* accounted for the largest number, being found in 83 per cent. Hookworm was found in 22 per cent. Multiple infections are frequent. *Diphyllobothrium latum*, *Trichuris trichiurid*, and *Enterobius vermicularis* are frequently seen. Liver flukes (*Clonorchis sinensis*), intestinal flukes (*Metagonimus yokogawai*), and lung

flukes (*Paragonimus westermani*) are occasionally encountered. Several localized endemic areas of *Schistosomiasis japonica* are found in certain parts of Japan. For the most part, the intestinal parasitic infections seen most commonly do not seem to affect the welfare of the children to any appreciable degree.

*Chronic Lead Poisoning.*—In 1892, Professor Hirota first described a so-called meningitis in infants. The cause remained obscure until 1924, when Professor Hirai discovered that it was a form of lead poisoning. A lead-containing face powder used by the nursing mother was the cause. This correlated with the age of greatest incidence, namely, 6 to 12 months. Basophilic granulation of the erythrocytes and the lead gum line led to the diagnosis. Following demonstration of the etiology the Japanese Government passed a law forbidding the inclusion of lead in face powder.

*Poliomyelitis.*—Cases have been seen, but they are sporadic rather than epidemic in form. From 1931 to 1940 the children's clinic at the Imperial University in Tokyo treated 685 patients. One hundred fifteen were under 1 year of age, 264 from 1 to 2 years, and 169 from 2 to 3 years. June, July, and August saw the largest number of patients. All of these patients had the paralytic type. A series of forty-nine patients with abortive poliomyelitis is also described.

*Japanese Type B Encephalitis.*—While this disease appears to have occurred as far back as 1871, it was first established as a characteristic entity in 1924. The mortality rate is as high as 60 per cent, mostly in older patients. The onset is abrupt, with high fever, headache, beclouded consciousness, and various degrees of paralysis. Complications such as pneumonia or urinary tract infections account for many of the deaths. The spinal fluid is clear but under pressure. The cell count is 25 to 500. At first, 50 per cent of the cells are polymorphonuclears; later, lymphocytes predominate. There is an increase in the total protein and globulin. Definite diagnosis can be established by demonstration of neutralizing antibodies and complement fixation reaction. Mouse inoculation is also employed.

In 1937, Segawa tested the neutralizing potentialities of blood sera of the inhabitants of Tokyo, dividing them into age groups. In newborns he found 78 per cent of sera contained neutralizing antibodies. In the age group of 1 to 3 years no neutralizing capacity was demonstrated. With increasing age the percentage again increased so that in the group from 40 to 60 years, 66 per cent of all sera sampled contained neutralizing antibodies.

*Miscellaneous Infections.*—Rat bite fever, leptospirosis, tsutsugamushi fever are encountered. Typhoid and paratyphoid fever occur at times. Leprosy is seen, and venereal diseases are common.

*Nutrition.*—It was not possible to obtain any definite information concerning the incidence of malnutrition and vitamin deficiencies among the children of Japan. Needless to say, many of them are subsisting on a diet both deficient in quantity and quality. Fukuoka, being a relatively small city in a fairly rich agricultural area, does not suffer acutely from the food shortage as do the large industrial cities of the main island of Honshu.

Superficial observations indicate that many children are underweight. The stunting effect of the diet seems to have been fairly well established. Reports of children being too weak to go to school were obtained. A longer period of study will be required to determine fully the results of the food shortage.

#### CONCLUSION

It is felt that a better understanding of the medical situation in Japan will ultimately improve the outlook for world peace. At no time in the history of that country have its people been more anxious to learn American methods. In medicine this is especially the case. A vacuum has been created with the collapse of German medicine, and we can determine to a great extent what will fill that space.

If American medicine can be brought to the Japanese in all of its fullness, so that they will assimilate not only the cold facts but also some of the higher spiritual aspects, then world peace will have been furthered. In this spirit the present account is offered

## Case Reports

### NEPHROSIS

#### A CASE TREATED WITH CONCENTRATED, LOW SALT, HUMAN SERUM ALBUMIN

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REFERENCES to the treatment of nephrosis with concentrated, low salt, human serum albumin have recently appeared in the literature.<sup>1, 2, 3</sup> We present this case as we believe it is the first so treated to be reported in the American pediatric literature.

F. M., a white male, aged 4 years, 4 months, was admitted to the New York Post-graduate Medical School and Hospital on Sept. 17, 1945, with a chief complaint of coryza of seven days' duration and edema of six days' duration. The boy had been in excellent health all his life until one week before admission. At that time, he developed a "running nose" and "slight cough" without fever. The following day his eyes and ankles were slightly swollen. The third day of illness, his abdomen and legs began to swell. The family history and past history were noncontributory.

The child's admission temperature was 99.4° F., his pulse was 82, respirations were 24, and blood pressure was 122/80. He was well developed and moderately well nourished, with generalized pitting edema and moderate dyspnea. The eyelids were moderately edematous. There was a mild pharyngitis with a postnasal drip. The heart was clinically negative, but there were medium, moist râles at both lung bases. The child's abdomen protruded moderately; there was a shifting dullness. Both lower extremities showed a 4 plus, pitting edema as high as the knees. The child weighed 49 pounds on admission; his weight before this sudden illness had been 36 pounds.

Admission blood count was within normal limits; the urine revealed 3 to 5 white blood cells per high power field, no red cells, an occasional hyalin and coarsely granular cast, and 2 plus protein. The nonprotein nitrogen was 60 mg. per cent and calcium was 8.3 mg. per cent. Serum protein values are given in Fig. 1 for comparison with later findings. Blood cholesterol varied between 500 and 600 mg. per cent.

The child was placed on a high protein diet (3 Gm. per kilogram of body weight per day) which was salt free. Fluid intake was 500 or 600 c.c. a day; output could not be measured because of incontinence.

Blood pressure findings repeatedly varied between 90/70 and 120/88. Urinalysis remained the same; at no time were more than 6 or 8 red blood cells present per high power field, and most of the time none were seen. An Addis count done one week after admission showed a marked increase in the number of casts, normal red, white, and epithelial cells. The nonprotein nitrogen remained normal.

Intensive therapy with ammonium chloride and magnesium sulfate failed to cause diuresis; the patient remained very edematous and weighed about 48

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pounds. Over a period of weeks 250 c.c. of blood plasma daily were also given, with no improvement. Whole blood transfusions were given as needed to maintain the red blood count and hemoglobin at high levels. The ascites increased to an extreme degree, so a peritoneal tap was done Nov. 28, 1945. The fluid lost by this procedure was rapidly replaced and the child was soon as edematous as before.

In the early part of January, 1946, adequate doses of thyroxin, ammonium chloride, and mercupurin were administered without effect. Urine showed 3 plus protein.

Early in February, a careful check was made on the food and salt intake. Although the child was offered a diet containing 3 Gm. per kilogram of body weight in twenty-four hours, because of his poor appetite, we were taking only .5 Gm. per kilogram. Although his diet was the accepted salt-free hospital diet (Table I), his daily salt intake was actually 1 to 2 Gm. a day. In addition,

TABLE I. SALT FREE, HIGH PROTEIN DIET WITH AND WITHOUT DIALYZED MILK AND AMIGEN

WITH UNDIALYZED MILK AND NO AMIGEN					WITH DIALYZED MILK AND AMIGEN			
MEALS	FOODS* (Salt free)	AMOUNTS	GM. PRO- TEIN	NaCl	FOODS† (Salt free)	AMOUNTS	GM. PROTEIN	NaCl
Break- fast	fruit juice	½ cup	1	.008	fruit juice	½ cup	1	.008
	cereal	¼ cup	0.5	.012	cereal (puffed rice)	¼ cup	0.5	.013
	(Cream of Wheat)				bread	1 slice	3	.023
	bread	1 slice	3	.023	butter	1 tsp.		.001
	butter	2 tsp.		.002	milk	1 cup	6	.068
	milk	½ cup	3	.260	amigen	2 tsp.	4	
					10 A.M.			
					orange juice		1	.008
					with 1 egg yolk and 2 tsp. amigen		3	.027
							4	
Noon meal	meat				meat (beef)	1 oz.	6	.051
	cheese				cheese			
	eggs				eggs			
	potato				potato	½ sm. one	1	.030
	vegetable				carrots	¼ cup	0.5	.013
	bread	1 slice	3	.023	bread	2 slices	6	.048
	butter	1 tsp.		.001	butter	2 tsp.		.002
	fruit				fruit			
	milk	1 cup	6	.520	milk			
	ice cream	½ cup	10	.233	ice cream	½ cup	10	.034
Night meal					amigen	2 tsp.	4	
	meat				meat (chicken)	1 oz.	6	.048
	cheese				cheese			
	eggs				eggs			
	potato				potato	½ sm. one	1	.030
	vegetable				vegetable			
	bread	1 slice	3	.023	bread	1 slice	3	.023
	butter	1 tsp.		.001	butter	1 tsp.		.001
	fruit	½ pear	0.5	.010	fruit	¼ cup	0.5	.004
	(canned pears)				(apple sauce)			
Bedtime	milk	½ cup	3	.260	milk	½ cup	3	.034
					amigen	1 tsp.	2	
Totals for day			36	1.636	milk	½ cup	3	.034
							68.5	.500

\*Food habits: Child refused meat, vegetables, and potato at both meals, which, if eaten, would have increased the protein intake and also raised the NaCl still higher.

†Refused vegetable at night meal.

he was receiving salt in the plasma and blood. Each 250 c.c. of plasma contains 1.05 Gm. of salt; each 250 c.c. of whole blood contains 0.58 Gm. of salt. He had not been given intravenous Amigen because each 1,000 c.c. of amigen contains 2.0 Gm. salt. Therefore, his daily salt intake was 2 to 3 Gm. The child was taken off all plasma and put on 50 Gm. of amigen daily by mouth. This was done by adding powdered amigen to grape juice flavored with lemon juice and sugar, and to orange juice. Amigen was also added to ice cream, jello, and custards. Despite this added protein offered, the child's total proteins could be raised to only 1 Gm. per kilogram of body weight in twenty-four hours, since he often refused the food that contained the amigen. Therefore, he was given 50 Gm. of amigen in fruit juice every evening by gavage. This was given in the

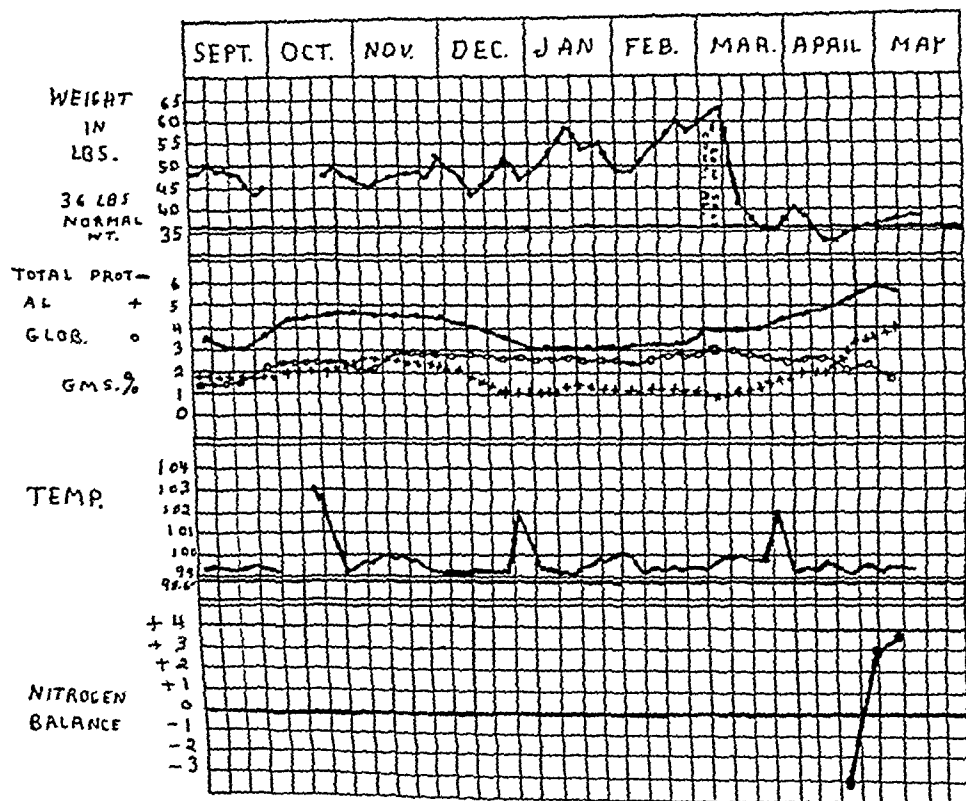


Fig. 1.

evening in order to prevent anorexia as much as possible. Even by this method, the total proteins were only 1.5 Gm. per kilogram of body weight. During this period the salt intake was 1 Gm. in twenty-four hours. This was lowered to approximately .5 Gm. per twenty-four hours by dialyzing the milk and by using fresh vegetable juices instead of canned vegetable juices. In addition, special attention was given to the removal of salt from all foods as far as possible, and special bread was prepared. Each 100 Gm. of canned vegetable juice contains from .060 to .080 Gm. salt. Each quart of undialyzed milk contains 1.72 Gm. salt, but by dialyzing the milk in the hospital, this value was brought down to .340 Gm. salt per quart of milk. A commercial preparation of dialyzed milk which contains .130 Gm. of salt per quart of milk may be used; it was used on this child during the last five days of his hospital stay (Table I).



The boy continued to be edematous and ascites was very marked. His protein intake was 16 Gm. daily, or about 1 Gm. per kilogram of body weight. The urine showed 4 plus protein, and 8 to 10 hyalin casts. The albumin-globulin ratio was inverted (Fig 1).

On March 8, 1946, the child was given his first dose of 15 Gm. of concentrated, low salt, human serum albumin by slow, intravenous drip. The albumin comes in 5 Gm. quantities in vials of 20 c.c., each of which has the osmotic equivalent of approximately 100 c.c. of citrated plasma. When injected intravenously, it draws approximately 70 c.c. of additional fluid into the circulation within 15 minutes, except in the presence of dehydration. The extra fluid reduces hemoconcentration and blood viscosity. One vial contains only 0.06 Gm. of sodium. Each vial of albumin was mixed with 30 c.c. of 10 per cent glucose to facilitate intravenous injection, since the albumin alone is very viscous. Therefore, three vials were dissolved in 90 c.c. of 10 per cent glucose. It is advisable to give the albumin solution at a rate not exceeding 15 drops per minute. There was no unfavorable reaction to the albumin.

This solution was given daily for two months. After three doses the child lost 9 pounds, the edema of the eyelids completely disappeared, the edema of the ankles diminished by 50 per cent and the ascites diminished greatly. The child's appetite improved remarkably. His protein intake went up from about 1.5 Gm. to 7 Gm. per kilogram of body weight in twenty-four hours. He lost all of his edema and his weight went down more slowly after the initial loss of 9 pounds in three days, but continued to go down consistently from 50 pounds to 34 pounds within two and one-half weeks (Fig. 1). At that time, he still had a mild amount of ascites. His weight then started to increase gradually. As proof that the child was having a true weight gain, a nitrogen balance test was performed. On April 18, 1946, during a twenty-four hour period, the total nitrogen intake was 9.5; nitrogen output was 12.6 Gm. The child was, therefore, in a negative nitrogen balance of minus 3. Pyridoxin was then given in a dosage of 50 mg. daily in an effort to promote better utilization of amino acids, especially tryptophan, and thus obtain a positive nitrogen balance. A nitrogen balance test done on April 30, 1946, showed that in a twenty-four hour period the child took in 11.4 Gm. of nitrogen and put out 8.4 Gm., and was in positive nitrogen balance of plus 3. The nitrogen intake was recorded daily and was found to be between 10 and 14 Gm.

During the two-month period that the child received the concentrated, low salt, human serum albumin, the urinary protein decreased to a value of 1 plus; very few white blood cells and no casts were found. Serum proteins were altered, serum albumin increased, and globulin decreased proportionately until a normal albumin-globulin ratio was obtained (Fig. 1). Blood cholesterol fell from 850 to 300 mg. per cent.

Since the child continued to improve, the low salt, human serum albumin was discontinued on May 3, 1946. He was kept in the hospital for eleven days following discontinuation of the drug, but when blood and urinary findings were not adversely effected, he was discharged on May 14, 1946. He received the high protein, salt free diet at home.

Follow-up examinations on June 12, and July 15, 1946, were made. The child weighed 40 pounds, temperature was normal, there was no edema or ascites, and the rest of the physical examination was normal. Urine tests revealed 1 plus protein, with no other abnormal findings; blood count was normal; total protein was 5.7 per cent; albumin, 3.5 per cent; globulin, 2.2 per cent; albumin-globulin ratio, 1.6:1; and cholesterol was 220 mg. per cent. The child leads the life of a normal, active, 5-year-old boy.

## COMMENT

This patient did not respond over a period of eight months to any of the accepted methods of treatment. His improvement was prompt and striking following the administration of concentrated, low salt, human serum albumin. In addition, he was on an especially rigid, salt free, high protein diet with dialyzed milk. He also received pyridoxin. Following the administration of pyridoxin, the patient went from negative nitrogen balance to positive nitrogen balance. We, therefore, believe that a rigid, salt free, high protein diet with dialyzed milk, and pyridoxine are valuable aids in the treatment of nephrosis. Naturally, further clinical studies are needed for a true evaluation.

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## ADDENDUM

Since this article was submitted for publication, four additional patients with lipoid nephrosis have been treated by one of us (A. G. DeS.) in the New York Postgraduate Hospital. The method of treatment has been the same as described herein. The patient whose case record was discussed in this article was last examined on Nov. 20, 1946. He is in excellent condition.

The second child so treated has also been discharged from the hospital. He is in good condition, free of any signs of edema, and in positive nitrogen balance.

The other three children are still in the hospital. They have been under treatment for periods of two weeks to seven weeks. All three are practically free of edema and show marked clinical improvement. Two of these patients had several peritoneal taps done in other hospitals to relieve marked abdominal ascites. It is interesting to note that none of our children treated with concentrated, low salt, human serum albumin required peritoneal taps after this treatment was started.

It is our impression that the results obtained in the treatment of lipoid nephrosis with the above outlined management are far better than with any other methods we have used heretofore.

A more detailed report of this clinical experiment with control studies will be published later.

## SYRINGOMYELIA, MORVAN'S SYNDROME

EDWARD B. HOLLEY, M.D.  
SALT LAKE CITY, UTAH

IN 1883 a report by Augustin Morvan<sup>1</sup> in the *Gazette hebdomadaire de medecine et de chirurgie* presented seven case studies which were considered to be examples of a new disease. Characteristics of the entity were loss of pain and temperature sensations of the extremities, amyotrophy, paresis, trophic disturbances of the phalangeal bones and joints and the skin overlying these areas, and mutilation of the fingers and toes resulting principally from painless, unnoticed trauma and infections. The etiology of this syndrome was not known to Morvan, but he expressed the belief that the source of the disturbance was to be found in the spinal cord. Chareot,<sup>2</sup> Joffroy and Achard,<sup>3</sup> and later, Kalindero and Martinesco,<sup>4</sup> presented evidence which led them to classify Morvan's syndrome as a chronic form of syringomelia, characterized mainly by trophic changes of bones, joints, and skin. To the present time, there have been no new concepts offered regarding the etiology or even the pathology, for as yet there have been no necropsy studies reported of patients who have died with this condition.

Since the initial discussion of this syndrome, infrequent case studies have been reported, in which the findings have paralleled to some degree those observed by Morvan. After a review of the available literature, a total of twenty-one case reports was found. Seven of these were included in the original report by Morvan.

Following are the summaries of the remaining fourteen cases, five of which were of adults and nine of children:

Yceland<sup>5</sup> reported a case of a 49-year-old, white male who complained of sores on the right hand. Some thirteen years previously he had observed painless whitlows occurring successively on the little, ring, and middle fingers and the thumb of the right hand. Sensations to pin-prick, heat, and cold were found absent on the right side of the face, neck, upper limb, and thorax as far down as the sixth rib.

Gate and Thevenon<sup>6</sup> described a case with bilateral anesthesia of the hands, contractions of the fingers into hooks, thick, hard, dry skin, and painless infections of the hands. There was a hypesthesia of the right hemithorax and right arm. The presence of a bilateral positive Babinski's sign was the only other abnormal finding of the physical examination. Roentgenograms which revealed an almost total destruction of the distal phalanx of the right thumb were the only abnormal laboratory studies.

Mandeville<sup>7</sup> presented the case of a 45-year-old, Negro female who had osteomyelitis of the left ring finger. Roentgenograms of the hand revealed destruction of the distal phalanx of the thumb as well as that of the ring finger. Two years later the patient complained of a cracking open of the fingers and loss of the finger nails. The following year, atrophy of the muscles of the hands and ulceration of the skin of the fingers were observed. Responses to pain and temperature stimuli were present at that time. The left upper extremity later revealed a brawny swelling of the skin with disuse of the arm. Roentgenograms revealed a Chareot's joint of the left shoulder. There was also atrophy of the distal half of the terminal phalanx of the left thumb and the tips of the terminal

phalanges of the left index, middle, and ring fingers. There was a persistent flexion deformity of the distal interphalangeal joints, giving the appearance of the "claw-hand" which has been occasionally described in cases of Morvan's syndrome. After several months of a painless, draining infection of the left thumb, a guillotine type amputation was performed on the left forearm. The limited pathologic report presented in this paper revealed nothing which clarified the nature of this disease.

Homans and Thanuhauser<sup>8</sup> have discussed the case of a 68-year-old, Italian male who demonstrated a reduced response to pain and temperature stimulation below the knees, ulcers and hyperkeratosis of the feet, mutilation of several phalanges with destruction and distortion of the metatarsal-phalangeal joints, and spontaneous fragmentation of some of the phalanges of both feet. All of the nails of the fingers and toes had an opaque appearance similar to frosted glass. The ulnar nerves were palpable as thickened cords without nodular or spindle-shaped deformities. There was a definite atrophy of the thenar and hypothenar areas and the interossei of both hands. The remainder of the physical examination was not unusual, and the laboratory results were not abnormal. It is doubtful that this represents an example of Morvan's syndrome. The patient had minimal sensory changes and palpable ulnar nerves, which indicate that the condition could be classified in that group of hypertrophic neuridites described by Dejerine and Sottas<sup>9</sup> in 1893.

The most recent report of Morvan's syndrome occurring in an adult was that of a 49-year-old, Negro female seen by Bloom and Moss.<sup>10</sup> This patient was perfectly well until the age of 43 years, when swelling and stiffness of the right upper extremity followed a relatively painless infection of the hand and arm. Shortly thereafter a similar swelling was observed involving the left upper extremity. Several painless ulcers then developed on the fingers. The wrist joints were crepitant but not painful when moved, and the range of motion was good. The response to pain and temperature stimuli was lost in both hands, but light touch and tactile sensations were normal. No muscular atrophies or fibrillations were observed. Roentgenograms showed old, disorganized fractures in both wrists, erosion of the terminal phalanges, soft tissue swelling, and "claw-hand." All laboratory studies were within normal range.

The remaining nine cases represent the total known occurrences of Morvan's syndrome in children. Parks and Staples<sup>11</sup> recently found seven cases in children in the European literature, to which they added two case studies of their own. All of these patients had an onset early in childhood. There was an almost equal involvement of the two sexes. The striking initial disturbance in these patients was the symmetrical loss of sensation to pain and temperature and later to touch sensations in the distal portions of all four extremities. These findings were followed by trophic disturbances of the skin, and atrophy of the bones of the hands and feet with resultant deformity of the nails. Finally, there occurred spontaneous amputations of digits or parts of digits due to the presence of infection. There was no paralysis, muscular weakness, or atrophy observed in these patients. Laboratory studies were not abnormal in any of them.

The following case report in a 2½-year-old child presents characteristic signs and symptoms not unlike those previously described, in which the disease first made itself evident at three months of age:

#### CASE REPORT

D. K., 2½ years of age, a white male, was admitted to the Salt Lake County General Hospital on March 1, 1946.

The infant was delivered spontaneously at term and appeared normal. The neonatal period and the two months which followed were not abnormal in any

way By the end of the third month, however, the nails of the toes and fingers had ceased to grow and three generalized, clonic convulsions occurred in a seven-day period. No trauma or illness was known to be present. Two months later the parents first observed that an older sister was walking on the fingers and hands of the infant without causing him any apparent pain or discomfort. The parents did not become alarmed because the hands appeared normal. At the age of one year the index finger of the left hand was found to be red, swollen, and warm. In spite of apparent soreness of the finger, the child was content to play as usual and used the finger as though nothing were wrong. When the finger was bumped, touched, or manipulated, the child did not cry out or object. No treatment was instituted, and after several days the redness and warmth disappeared, but much of the swelling remained. Six months later a similar painless involvement of the left middle finger was noticed. The local physician was consulted, and the finger was incised. No anesthesia of any kind was used. In spite of this, no sign of distress was expressed by the patient. A small amount of purulent material escaped from the incision and there was very little bleeding. Three months passed before the wound was completely healed. Coincidentally, it was noticed that the nail of the still swollen and somewhat clubbed index finger was much more irregular, convex, and smaller than its fellow of the other hand. The skin of the hands was tough, dry, and firm.

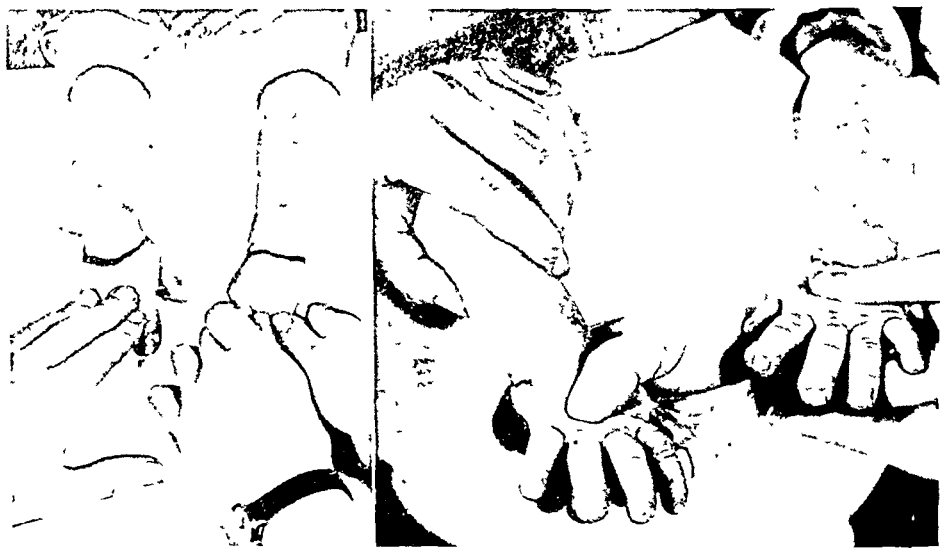


Fig. 1A.

Fig. 1B.

Fig. 1A.—Line at wrists indicates limit of area of complete anesthesia. Hypesthesia is present to elbows. Trophic disorder of skin of forearms is shown

Fig. 1B.—Demonstrating blunt terminal phalanges and "claw-like" deformity of left hand.

There were no new developments until five weeks before the next admission. At that time, the patient was admitted to a local hospital with pneumonia. Sulfonamide therapy was instituted, and the response was satisfactory. While in the hospital the child became very irritable, and at times was seen biting his wrists and forearms. The wounds nearer the wrists were deeper, but seemed to be much less painful than those near the elbows. Markings from the bites were still very distinct at the time of discharge from the hospital. Two weeks later, similar markings had appeared high on the arms, and the old areas on

the forearm were much more evident, yet no one had seen him biting himself. A deep laceration was discovered in the distal interphalangeal fold of the left index finger. When the laceration was cleaned and dressed, very little bleeding occurred and the child did not resist or cry. After several days, the laceration had not begun to heal and the markings on the arms and forearms seemed to be spreading. Because of these disturbances the parents brought the child to the Salt Lake County General Hospital for diagnosis and treatment.

His development had been moderately retarded. The patient sat at age 9 months, crawled at age 15 months, began to stand at 18 months, and had walked two or three steps at a time for the previous two months. The child's diet had been adequate and satisfactory in all respects. Immunizations for diphtheria and tetanus were completed in December of 1945. The family history was noncontributory.



Fig. 1C.—Limit of hypesthesia is indicated by line above toes.

Physical examination at the time of admission revealed a rectal temperature of 99.8° F.; the pulse was 100, and the respiratory rate 22 per minute. The systolic blood pressure was 88 and the diastolic 58. The height was 33 inches, the weight 24 pounds, and the occipital-frontal circumference 18 inches. The child did not appear acutely ill or distressed. The body size and proportions appeared normal, and the nutrition was good. The patient played cheerfully in the presence of his parents, but soon became irritable when strangers appeared. All tasks requiring the use of the fingers were accomplished with a great deal of difficulty and were awkwardly performed. Except for a mild rhinopharyngitis and hypospadias, the positive findings of the physical examination were limited to the extremities. There were scattered, bright pink, superficial lesions on the dorsal surfaces of the upper extremities from the wrists to the shoulders. These were round or oval in shape, 0.8 to 2.5 cm. in diameter, and had a fine bran-like desquamation near the periphery. The lesions apparently did not itch. The skin of the hands was very dry and thickened, especially on the fingers near the nails and around the old laceration of the left index finger. The margins of the laceration appeared thickened and keratotic, and no granulation tissue could be seen in the wound. The nails of the clubbed index and middle fingers of the left hand were convex and curved over the ends of the fingers. Both nails were much smaller and thicker than those of the corresponding fingers of the right hand. The other nails were wrinkled, thickened, concave, and wider than they were long. The nails of the toes were more normal in shape, size, and thickness, and the skin of the heels and toes was dry

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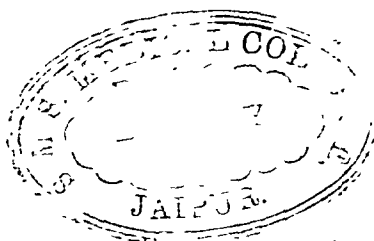
There was very little change in any of the findings during the thirty-six days of hospitalization. The skin lesions and laceration of the left index finger were much the same at the time of discharge as they were at the time of admission. The child was frequently seen pushing the lacerated finger back and forth across the teeth, causing it to bleed. This did not appear to be painful. The patient could sit, stand, and crawl, but could not walk at the time of admission. A total of ten words were used by the patient, and none of these were ever used in combinations. The entire hospital stay was uneventful, and the patient was discharged to his home on the thirty-sixth day.

#### CONCLUSIONS

A review of the literature has revealed a total of twenty cases of Morvan's disease. A case of Morvan's syndrome occurring in a 2½-year-old male is presented. This child is believed to be the youngest yet reported.

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and thick, but elsewhere was not abnormal. The joints of the lower extremities exhibited an exaggeration of range of motion, and the muscles were soft and flabby to palpation.

All of the superficial and deep tendon responses were hypoactive. No pathologic responses were elicited. No muscle weakness, fasciculation, atrophy, or paresis was observed. Except for the fingers, the extremities were symmetrical. There was a definite, bilaterally symmetrical, glove-like area of anesthesia to pain and temperature stimuli. There was a similar lack of response when these same areas were touched with cotton. Areas of hypesthesia extended from the wrists to the elbows, with the greatest reduction of sensation perception distally. Above the elbows there was little if any change observed. Similar disturbances were found in the lower extremities, but to a lesser degree. The toes demonstrated a rather marked hypesthesia to pain and temperature, but response to light touch was present. There was a progressive increase in the degree of response to pain and temperature stimulation to a level just below the knees. All other body areas were apparently not involved.

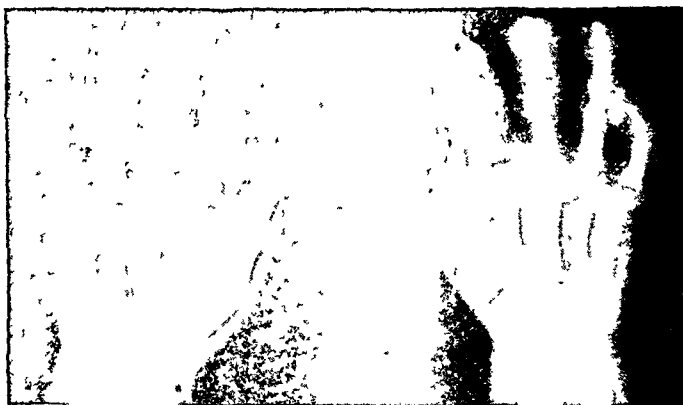


Fig. 1D — "Claw-like" deformity of left hand is shown. There is no change in bone structure.

Repeated blood studies and urinalyses were normal. All blood cultures remained sterile and blood agglutinations were negative. The blood serum calcium was 10.9 mg. per cent, and the serum phosphorus level was 4.4 mg. per cent. The Mantoux and Kahn tests were negative. Repeated cultures taken from the skin lesions and scrapings obtained from the nails and the laceration of the left index finger were not remarkable. Following is the interpretation of the roentgenograms by Dr. Henry H. Lerner, Head of the Department of Roentgenology of the University of Utah School of Medicine:

"Both hands: There is delayed appearance of the secondary centers of ossification of the metacarpal bones and of the phalanges. There is a "claw" deformity of the left hand with marked inversion of the fifth finger. The bone structure is normal.

"Both feet: There is a delay in the appearance of the secondary centers of ossification of the metatarsal bones and phalanges. Both fifth toes show the presence of only two primary centers of ossification for the phalanges. The middle ossification center appears to be missing.

"There is obvious delay in the development of the secondary centers of ossification. The findings place this child in the tenth percentile class (slow) according to the method of Vogt and Vickers."

There was very little change in any of the findings during the thirty-six days of hospitalization. The skin lesions and laceration of the left index finger were much the same at the time of discharge as they were at the time of admission. The child was frequently seen pushing the lacerated finger back and forth across the teeth, causing it to bleed. This did not appear to be painful. The patient could sit, stand, and crawl, but could not walk at the time of admission. A total of ten words were used by the patient, and none of these were ever used in combinations. The entire hospital stay was uneventful, and the patient was discharged to his home on the thirty-sixth day.

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# The Academy Study of Child Health Services

*Note: The central office of the Study of Child Health Services has moved to 2346 Massachusetts Avenue, N.W., Washington 8, D. C.*

One of the outstanding characteristics of the current Study of Child Health Services is the broad scope of its inquiry. Many excellent and detailed surveys of child health have been made in local areas dealing with limited aspects of the entire field, but never before has there been a similar attempt to gather information pertaining to child health on such a wide scale at one time. From the previous, rather specialized investigations it has been impossible to gain an over-all picture of the situation such as that which is sought by the Academy Study.

When the study was first being organized, there was considerable discussion concerning the advisability of carrying it out on a sampling basis throughout the country. Intensive study of facilities and services in certain selected areas would have greatly simplified the conduct of the study and would have decreased the amount of work involved. The sample technique was abandoned, however, in view of the fact that one of the fundamental purposes of the study has been to stimulate local groups to evaluate services for child health in their own communities. A sampling study would not have yielded sufficiently detailed information for community analysis on a nationwide scale.

In the conduct of the Academy Study, pediatricians, other physicians, and dentists, by virtue of filling out their own questionnaires, have had an opportunity to become familiar with some of the forms used in collecting the desired information. They will thus have become aware of the Series III schedules relating to physicians and dentists in private practice, and some physicians will also have reviewed or assisted in the completion of some of the Series I schedules designed for hospitals and institutions. Although the Series II and IV schedules have been mentioned briefly in earlier articles dealing with the study, the exact content and coverage of all the series have not been published in any detail. It may be of interest to the individual pediatrician and physician, therefore, to learn that the particular schedule which he filled out and returned represents only one of a total of twenty-three schedules. In order to dispel the belief that the questionnaires for those in private practice constitute the full extent of the study, and as a means of indicating the actual scope of the project, a more complete description of all the schedules is presented.

The twenty-three schedules mentioned are divided into four major categories or series representing the four fields of inquiry covered by the study:

## SERIES I

Series I schedules seek information regarding facilities, services, and personnel available in hospitals and other institutions which admit children. This series includes eight schedules in all, which are identified as follows:

*Schedule I-A. Information on Pediatric Hospitals, General Hospitals and Other Hospitals With Maternity Facilities.*—This four-page schedule contains twenty-nine questions including such items as type of ownership, admission policies, type of administration, services rendered, capacity and physical facilities, medical and nursing staff, and departmental organization. This schedule was designed for use in those states where the Commission on Hospital Care Survey did not coincide with the Academy Study.

*Schedule I-B and I-C.*—In states where a survey under the auspices of the Commission on Hospital Care was in process at the same time as the Study of Child Health Services, information for Schedule I-B was collected in cooperation with the Commission and Schedule

IC was completed by the transcription of data from the Commission schedules. Thus the data contained in Schedules IB and IC combined are identical with those included in Schedule IA.

*Schedule I-D. Supplementary Information on General, Pediatric and Maternity Hospitals With Twenty-Five or More Beds.*—In preparing the schedules for the hospitals, an attempt has been made to introduce qualitative as well as quantitative values. For this purpose, the cooperation of the pediatricians themselves has been obtained. Physicians who are familiar with pediatric practice are obviously best qualified to evaluate hospital services for children. Hence, Schedule ID was prepared with the thought in mind that it should be filled out by a pediatrician at the time of a personal visit to the hospital. This schedule may therefore be considered as a supplement to Schedule IA, adding qualitative values which would otherwise be lacking.

*Schedules IE Through IJ* all relate to special hospitals. Each of these schedules consists of four pages containing items specifically concerned with the accommodations, services and facilities for care of children in the following special fields:

*Schedule I L. Nervous and Mental Hospitals, Including Institutions for the Feeble-Minded.*

*Schedule I F. Tuberculosis Hospitals; Sanatoriums and Preventoriums Admitting Tuberculous Patients.*

*Schedule I G. Convalescent and Chronic Hospitals, Rest Homes and Nursing Homes.*

*Schedule I H. Contagious Disease Hospitals.*

*Schedule I J. Orthopedic Hospitals*

## SERIES II

Series II includes eight different schedules all concerned with services and facilities for child health provided by public and private health organizations and agencies.

*Schedule II. Summary of Public Health Services Available for Children.*—As its title indicates, this schedule gives a summary of all official health services for children available in each county, city, state, or local health district.

*Schedule II A. Medical Well Child Conferences.*—A copy of this schedule is being completed by each agency or organization which conducts well child conferences. The items include admission policy, detailed information concerning types of clinics, personnel, number of sessions held, number of patients seen, type of service rendered, and the location of the conferences.

*Schedule II B. Dental Services for Children*—The information sought by IIB is similar to that concerning the well child conference, including a breakdown of the type of dental service rendered to children over a one year period.

*Schedule II C. Mental Hygiene Services for Children.*—Admission policy, specific data on types of cases and services rendered during a one year period, personnel on staff, and amount of service to other agencies such as schools and welfare organizations illustrate the type of information being obtained on this schedule. The type of cases for which information is sought include mental deficiencies, psychoses, convulsive disorder, delinquents, and behavior problems.

*Schedule II D. Health Services for Physically Handicapped Children.*—In addition to background information, IID is concerned specifically with the number of children and the types of cases seen during one year, including orthopedic, poliomyelitis, cerebral palsy, rheumatic fever, and heart disease. Special attention is paid to the number and work status of professional staff personnel supplying these services.

*Schedule II E. Communicable Disease Control.*—IIE includes data on number of immunizations for smallpox, diphtheria, whooping cough, and typhoid, personnel administering service, and special information concerning services by official health agency in relation to communicable disease control.

*Schedule II F. School Health Services*—IIF covers such items in the school health program as medical examinations, special examinations including vision, hearing, and tuber

culo- tests, special services relating to nutrition, psychiatry, speech and so forth, medical and nursing personnel available, nursing services provided, and number of children served by program

*Schedule II G Public Health Nursing Services*—II G relates to the extent and types of nursing service rendered during a one year period, including number of nurses and the types of programs in which they participate

### SERIES III

Since the three schedules included in this series have been described and distributed widely throughout the country a detailed description is not needed here. By now almost every physician and dentist in the country will have been at least exposed to one of the three forms which include

*Schedule III A Physicians in Private Practice.*

*Schedule III B Pediatricians in Private Practice*

*Schedule III C Dentists in Private Practice*

### SERIES IV

This series of schedules is a fairly recent addition to the study list. So far only two of the proposed three schedules to be included in this series have been developed in final form.

*Schedule IV 1 Pediatric Education in Medical Schools*—The first of the detailed schedules dealing with pediatric education is a ten page folder covering all aspects of undergraduate teaching in all medical schools in the United States. Since this is the first description of these schedules to appear, a complete outline of the contents is presented to illustrate the intensive nature of this important part of the Academy Study.

The main headings of this schedule are as follows

- 1 Name and location of medical school
- 2 Enrollment of last ten classes
  - a Enrollment in each of the four academic grades.
  - b Number graduated
  - c Number of applicants and per cent qualified for admittance to school
- 3 Requirements for Admission (excluding wartime accelerated program) including acceptance of women and Negroes
- 4 Organization of Department of Pediatrics, including subjects taught and by which department.
- 5 Staff of department (active), including hours per school year devoted by staff members to various teaching activities
- 6 Budget (1946-47), showing source and amount of funds for teaching, research, and other activities
7. Student hours in pediatrics
  - a Proportion of time devoted to pediatrics during each of four academic years
  - b Detailed analysis of subject matter covered, method used, and activities and/or services performed by junior and senior students
  - c. Amount of time and duties of clinical clerkship
8. Opportunities for observation and practice in care of normal newborn, prematures, special handicaps, convalescents, dental patients, and patients in specialty clinics
9. Public health activities. Participation of junior and senior students as observers or workers in child health conferences, school health and nursery school programs, children's institutions, etc.
- 10 Clinical facilities used for teaching.
  - a. In patient facilities. Number of children's beds used for teaching, by type of service in each hospital affiliated with a medical school.
  - b. Out patient facilities. Number of child patients and total children's visits

11. Special opportunities for work with social service departments on social aspects of disease and on use of community facilities.
12. Facilities available for pediatric pathology.
13. Textbooks used.

*Schedule IV-B. Pediatric Education in Hospitals Approved by American Medical Association for Pediatric Residences and Fellowships.*—Whereas Schedule IV-A is concerned with the undergraduate teaching of pediatrics in medical schools, Schedule IV-B is intended to evaluate the teaching received by assistant residents, residents, and fellows in the teaching hospitals throughout the country. It would be desirable to include in this portion of the Study all hospitals which have been approved by the American Medical Association for pediatric internships as well as assistant residences and residences. There are so many institutions approved for internships that the amount of effort involved including these did not appear justified. This schedule, therefore, deals primarily with the training received by those who will ultimately become pediatricians.

The items included in this schedule may be summarized as follows:

1. Identification of the hospital with designation of type of ownership and control, and medical school affiliation.
2. The house staff active on the pediatric service.
3. The clinic facilities available for teaching, including premature and newborn care.
4. The number of pediatricians responsible for teaching the house staff, whether on full or part-time and whether or not certified by the American Board of Pediatrics.
5. The number of autopsies and the extent to which residents assist in the pathologic work.
6. The responsibility for routine laboratory work on the part of student, intern, assistant resident, resident, fellow, or technician.
7. Detailed description of the types of experience available to residents on the pediatric service, both in patient and out-patient.
8. The type of well child service in which the residents participate.
9. The number of hours spent by residents in teaching conferences, discussion groups, ward rounds, etc.
10. The amount of opportunity available for training in pediatric specialties.
11. The amount of teaching which is done by the assistant residents and residents themselves.
12. Opportunities for research.
13. The responsibility of handling records.

*Schedule IV C. Postgraduate Pediatric Teaching.*—This schedule has not yet been prepared in final form. It will be based upon the desire to include in the study information on the quantity and quality of postgraduate teaching, and refresher courses.

When this formidable mass of information is gathered, analyzed, and digested, abundant factual data will be available upon which to base sound plans for the improvement of child health.

# The Social Aspects of Medicine

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## THE UNITED STATES PUBLIC HEALTH SERVICE AND THE DEVELOPMENT OF FEDERAL PARTICIPATION IN HEALTH CONTROL

The communication which follows is a rough resume full of paraphrase and quotation of a part of Harry S. Mustard's recent book on "Government in Public Health".\* The latter gives the history of the development of the various health services in the United States, the local health departments, the state departments of health, and the Federal Health Services, and then describes the status and interrelationships of each in so far as the latter can be defined. His book, which is exceedingly intelligent and interesting, makes one feel that the organization of the Health Services in the United States is as complicated as the English Constitution and, like the latter, is the result of indigenous disconnected growths determined by health problems peculiar to time and place and later brought together and united by a catch as catch can process into a working arrangement. Apparently, health administration in this country sprang up locally and state and federal supervision and control were later developments, the latter following the former. Of the system of health administration as it exists today Dr. Mustard writes, "Not by the greatest stretch of the imagination and sympathetic understanding can it be said that the situation is as it should be. It violates design, it is diffuse, it inhibits coordinated action and invites confusion. And yet, amazingly enough, the individual federal health services function quite efficiently in their respective spheres, and if there is no order in the existing arrangement, there are at least explanations for it." As one reads Dr. Mustard's book, the present system seems to have one advantage, namely, that, with all its obvious imperfections, it possesses great flexibility which permits adjustment to the special needs of localities. This flexibility is due to the loose joints between federal, state, and local control and the ill defined interrelationships which permit a wide latitude of interpretation and action.

Before proceeding to our special topic, it may be wise to point out that forty other federal agencies participate to some degree in public health or medical care activities. The most important of these are scattered in the Departments of Agriculture, Commerce, Interior, and Labor, and in the Federal Security Agency.

Although I have stated that the Federal participation in the public health services of the country was a late development, the Public Health Service itself dates to 1798. It was born in a manger, so to speak, for at the time of its birth it was a tiny, insignificant pre-mature and nobody conceived how it would grow or what it would become. The seal of the United States Public Health Service consists of a fouled anchor on which is crossed a Caduceus with the date 1798 inscribed below. "That the Caduceus refers to the healing art is obvious, the fouled anchor represents the sailor in distress, and the date indicates the date of enactment of the first Federal law relating to medical care of merchant seamen." As a matter of fact, Alexander Hamilton prepared a report to Congress in 1792, recommending the establishment by the Federal Government of one or more Marine Hospitals as a measure in the interest of humanity in order "to protect from want and misery a very useful and, for the most part, a very needy class of the Community (the sailors of the Merchant Marine)." A bill to this effect was brought before Congress in 1798 by Mr. Livingston of New York. According to it, the relief of the seamen was to be financed by the deduction of twenty cents per month from the wages of each. The President was empowered to appoint Directors of Marine Hospitals in the several ports of the United States and it was the duty of these directors to arrange for hospitalization and provide care for this

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\*Government in Public Health Harry S. Mustard, New York City, 1945, The Commonwealth Fund

particular group and to build Marine Hospitals. No salary was provided for the directors but they were to be reimbursed from Federal funds for necessary expenditures incurred. Each director was responsible to the local Collector of Customs who, in turn, represented the President of the United States. In regard of this act, Falk has written as follows: "This oldest medical service is significant in three respects: (1) it was established for self-supporting, not dependent persons—Americans, seamen and the personnel of the Navy; (2) it was financed by a tax on seamen, by pay roll deductions from the pay of officers, seamen, and marines in the Navy, and by general taxation; and (3) it included treatment by private physicians and hospital care. As long ago, then, as 1798-99, the principle was accepted that the Federal Government should provide tax supported medical services and hospitalization for certain classes of independent (non relief) persons under what was one of the first systems of compulsory sickness insurance in the world." However, as Mustard points out, neither the author of the bill nor the Fifth Congress which passed it, had the clairvoyance to envision and anticipate the great problems in medical care which would come up 150 years later, and the question at issue in their minds was one of expediency in meeting an insignificant problem and not of establishing the foundation of a national system. It is interesting that the bill excited some powerful opposition. Mr. Sewell of Massachusetts doubted the propriety of taxing seamen only for the support of what ought to be considered a public charity. Mr. Varnum of Massachusetts expressed the view that, "It was a business which more particularly concerned the legislatures of the individual states." Mr. Gallatin "was against providing a fund for the purpose by a tax upon labor, which would, in all respects, be a capitation tax." Mr. Pinkney of South Carolina, who supported the bill, thought it "only reasonable and equitable that the sailors should pay for the benefit which they were themselves to receive and that it would be neither just nor fair for other persons to pay it." I have gone into this early history in some detail because of its antiquarian interest and, also, because it shows that the legislators then had the same differences of opinion as the physicians today. It is worth noting, also, that the issue was not decided wholly or perhaps chiefly on its intrinsic humanitarian merits but as the result of political expediency. It seemed wise to cultivate and enlarge that useful group of labor and with that end to enact a policy which was an innovation and perhaps an exception never to be repeated.

The act was passed in 1798 but the following year was amended "to provide similar benefits, on a likewise required payment of twenty cents a month, to each sailor and officer of the navy, including the marines. Also, funds collected in one port could be used for relief in another. Apparently, only fragmentary records of development were kept during the first seventy five years of the Act for the Relief of Merchant Seamen, and such reports as exist indicate that the work did not progress well. Factors contributing to the situation have been summarized by Leigh. "During its first seventy years of activity, the Service had acquired practically all the administrative disabilities associated with Jeffersonian and Jacksonian democracy, its personnel was the object of party spoils, its purchase of supplies was an adjunct to party machinery; its decentralization and lack of central supervision was almost complete; its hospitals were a part of the annual distribution from the Congressional pork barrel; as a means of governmentally supervised sickness insurance it was a fiscal failure requiring annual doles from Congress to keep it solvent and functioning; on account of enforced parsimony it was also very far from offering any guaranty of medical aid to the sailors even at the principal ports."

In 1869, Mr. George S. Boutwell arranged for John Shaw Billings, then a medical officer of the army, to investigate and make recommendations concerning the Marine Hospital Service, and on the Billings-Stewart report was built the act of 1870 by which the Service was reorganized and erected on a national basis. The newly proposed legislation was designated "an Act to reorganize the Marine Hospital Service and to provide for the relief of sick and disabled seamen." It was proposed that the amount deducted from the seamen's wages be increased to forty cents a month, that nationalized supervision under medical auspices be provided, and that a supervising surgeon be appointed. Opponents of the bill could see no possible reason for employing a chief medical officer who would be paid a salary to travel over the country at the Government's expense, but the act was passed and



from the administrative standpoint a national service was created. The directing officer appointed happened to be a very able man, Dr. John Woodworth, who had been in health work in Chicago and had served as a surgeon in the Federal Army in the War between the States. He organized the new Corps and its procedures along military line. "He insisted upon searching and impartial entrance examinations, rather completely removed tenure of office and promotion from politics and instituted other sound measures that remain in effect today. In his report of 1874, he devotes a section to "Preventive Medicine in the Service." He wrote, "While the primary object of the Service as defined by statute is the relief of sick and disabled seamen, the duty of preventing, in whatever degree, such sickness and disability is also conceived to be within its scope. Hence preventive medicine, which is receiving from the profession a continually increasing amount of attention, has not been lost sight of in its bearing upon the physical welfare of seamen; and the medical officers of the Service have been invited to study and report upon the conditions of sea life with a view to devising measures for the preservation of the sailor's health and his protection from disease."

The requirement that beneficiaries of the Maine Hospital Service contribute to its support was eliminated by an Act of June 26, 1884. The expenses were to be paid by a special tonnage tax and general taxation. The tonnage tax was eliminated in 1905 and the funds were supplied by the Treasury Department. The system of indirect and contract medical service has become strongly centralized. Part time physicians have been replaced by full time medical officers upon a career basis. The beneficiaries were made to include merchant seamen, coast guard personnel, coast guard dependents, coast and geodetic personnel, and a long list of others.

Though the Act for the Relief of Sick and Disabled Seamen was the first Federal Legislation that provided medical care for a certain group of the civilian population, it is generally considered as the nucleus around which the United States Public Health Service developed. However, other laws were passed, giving the Federal Government special nationwide responsibilities. One act, passed in 1796, provided for Federal cooperation with States and localities in enforcing state and local quarantine relating to ships. Quarantine was regarded as a State function. This act furnished the Federal Government with a basis of authority for making uniform the quarantine procedures at the various ports in the United States. Many members of Congress, however, expressed themselves as being convinced that "Each independent state had a right to legislate on this question for itself. However, constant recurrence of yellow fever epidemics, the memory of the cholera in 1882 and 1873, caused public opinion to demand national enactment in order to prevent the introduction of contagious diseases through the ports. The result of all this was the creation in 1879 of a National Board of Health to have charge of interstate and foreign quarantine. There developed strong opposition to the National Board of Health after its establishment. Dr. Joseph Jones, President of the Louisiana State Board of Health, spoke of "The insolent pretensions of National Board of Health with its odious system of espionage and meddling." But the chief opposition came from the Maine Hospital Service itself, which had been deprived of its quarantine responsibilities. The National Board of Health went out of existence in 1893 after four years, and the quarantine duties were restored to the Maine Hospital Service. 1893 Congress gave the Federal Government further powers, ruling that the regulations of quarantine followed by the various States and ports must be pursuant of or consistent with the Federal law. This Act of 1893 further made provision that if State or municipal health authorities did not have adequate laws, the latter would be supplemented by Federal laws, and if they failed or refused to enforce proper rules and regulations, the Federal Government would have power to supersede them. All State and municipal quarantine stations have been purchased by the Federal Government and all foreign quarantine in the United States is now conducted by the Federal Government.

I have given a brief and fragmentary summary of the history of the development of the United States Public Health Service and of the growth of Federal power in health administration in the country, as recounted by Dr. Mustard, because it is interesting to understand how and why they originated and to realize that the increase in Federal power

by a process of leaps from nil at the beginning has been the result of social and economic necessity. A Federal service of medical care was developed to look after seamen of the Merchant Marine. It was Federal by necessity because the seamen as a class were wanderers and the problem of their care could not be met by the individual states. When the service for seamen was established as a Federal institution, it was easy and natural to extend it to other groups, for example the navy and the marines. As soon as it became apparent that the municipalities at the ports on the eastern seaboard and the states themselves with their varying regulations and systems of operation could not prevent the introduction of yellow fever, cholera, plague, and other diseases, the Federal Government was obliged to intervene for purposes of efficiency by giving itself increased powers. Again it turned to the Marine Hospital Service as the only existing Federal Medical agency. Thereafter, as other problems arose, necessitating unified operation and control or better coordination, laws were passed increasing the Federal prerogatives and at the same time increasing the powers and the scope of action of the United States Public Health Service. And when, finally, Congress embarked on a policy of grants-in-aid to the different states, it turned to the United States Public Health Service and, also, to the Children's Bureau, the latter being a recent development. Now the authors of the Wagner-Murray-Dingell Bill have designated the United States Public Health Service as the agency for the administration of its medical care program on a nationwide basis.

Though we may look askance at the growth of Federal power in this country, in matters pertaining to health and in other things, we are compelled to see that Federal power in public health matters has been increasing ever since this country began. As the country becomes larger and its organization more complicated, increased centralization with its advantages in planning and operation becomes an economic and social necessity. Wherever one looks in Europe, federal governments are being vested with increased power. The social and economic revolution which we are now witnessing and in which we, ourselves, are beginning to be involved, is taking the same form the world over, and in this country has attained far less development than in war-torn Europe with its miseries. But we might as well accept the evil, if you wish, as a fact that the increase in the power of the Federal Government is a world trend, and with new ideas, which carry with them dreams, that medical care can be brought to everyone as his inalienable right. With the advance in medical knowledge and technology, which make such ideas and dreams realizable, increased central direction has become mandatory.

I do not wish to imply that there is or should be no limit to assumption of Federal power in health matters. It seems to me wise to limit it as much as we possibly can without the sacrifice of efficiency and to endeavor as tenaciously as possible to retain the present balanced system of Federal, State, and local health services, which as already pointed out, have great adaptability and latitude though seeming at times intolerably cumbersome and inefficient. After all, they are founded on experience and we ought to hesitate a long time to exchange a system founded on experiences for one founded on theory.

Incidentally, it is interesting to pediatricians to note that a Federal Bureau of Health did exist for four short years and that the United States Public Health Service (the then Marine Hospital Service) was accessory to its murder. It is also interesting to note that the same problems which exist today in regard to the participation of Government in medical activities and the proper means for their support were thought of and discussed by the founders of this country 150 years ago, and that 150 years ago the Federal Government quite unconsciously and in all innocence performed an experiment in medical care which was a poor affair and a failure but had great and splendid consequences.

E. A. P.

## Academy News and Notes

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Two members of the academy have been released from service:

Seymour Fisher, Vt Benjamin Harrison, Ind (*Army*)  
Thomas M Lamb, Brooklyn, N. Y. (*Army*)  
Daniel J Pachman, Chicago, Ill (*Army*)  
Samuel Jacob Werlin, Troy, N. Y (*Army*)  
Lummett E Sappington, San Francisco, Calif. (*U.N.R.R.*)

Dr Albert P Knight who was released from service in the Army, was formerly from Waverly, N Y and is now in Tokyo, Japan, in the capacity of Pediatric Consultant to the Department of Public Health and Welfare of General Headquarters of the American Forces Pacific Area

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## News and Notes

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The following physicians have been certified in the Sub Specialty of Allergy by the American Board of Pediatrics in cooperation with the Committee on Allergy of the American Board of Internal Medicine all certified on record without examination:

Oscar M Schloss, 125 E 72nd Street, New York City, N. Y.  
Lewis Webb Hill, 319 Longwood Avenue, Boston, Mass.  
William Potter Buffum, 122 Waterman Street, Providence, R. I.  
Bret Ratner, 50 E 78th Street, New York City, N. Y.  
Jerome Glaser, 300 S Goodman Street, Rochester 7, N. Y.  
Joseph Harman Fries, 25 Plaza Street, Brooklyn 17, N. Y.  
John E. Gundy, 264 King Street, Port Chester, N. Y.  
Arthur J. Horeish, 10515 Carnegie Avenue, Cleveland, Ohio  
Samuel J. Levin, 469 Fisher Bldg., Detroit 2, Mich.  
W. Ambrose McGee, 1601 Monument Avenue, Richmond 20, Va.  
Benjamin Zohn, 1449 Union Street, Brooklyn 13, N. Y.  
Orlando L. Ross, 9 Exchange Place, Salt Lake City, Utah

Dr. Helen B Tausig and Dr Alfred Blalock will together deliver the fifteenth annual series of the Benjamin Knox Rachford Lectureships on Tuesday evening, Feb. 18, and on Wednesday evening, Feb 19, 1947, at 8:30 P M, in the auditorium of the Children's Hospital Clinic and Research Building, Cincinnati, Ohio The general title of their lectures will be "Diagnosis, Surgical Treatment, and Results in Congenital Heart Disease."

## Book Reviews

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**Medecine Social de L'Enfance et oeuvres de protection des premier age.** Dr. Lucien Garrot, Liege, 1946, Editions Desoer, 364 pages.

A history of the infant welfare movement in Belgium, its development, present status, and a discussion of needs and plans for the future by the medical counsellor of the l'Oeuvre National de l'Enfance. The text discusses infant mortality, its causes and its relation to social conditions. A large part is devoted to the problems and work for the protection of infants in Belgium. One finds that even in so small a country as Belgium where infant health and welfare work is in part private and in part state, there are marked inequalities in the character of the service similar to the conditions which prevail in our own country.

B. S. V.

**The Compleat Pediatrician.** Fifth Edition. W. C. Davidson, Durham, N. C., 1946, Duke University Press. Price \$3.75.

The fact that this is the fifth edition of the *Compleat Pediatrician* since 1934 testifies to two matters—first, that the practicing pediatrician and physician has found it a most valuable book for rapid reference, and second, that the author has kept pace with the rapid changes in medical knowledge. In this fifth edition the chief changes are in the section on chemotherapy, infectious and tropical diseases about which so much new information and knowledge came out of World War II.

**Clinica Y Laboratoria.** Dr. Gustave Pittaluga (Professor at the institute for scientific investigation of the University of Havana), Havana, 1906. M. V. Freneda, 459 pages.

A text of clinical laboratory methods with chapters devoted to the blood, urine, serology, functional tests for the liver and kidney, basal metabolism, etc. The bibliography following each chapter shows a thorough knowledge of American as well as Spanish literature.

**Acrodynia Infantil.** A. Ballabugua Aquado (Chief of the service for infants at the pediatric clinic of the University of Barcelona), 1946, Zaragoza, 95 pages.

A monograph on acrodynia, discussing the etiology, pathology, and clinical manifestations of the disease, with an excellent bibliography of over 250 references.

**Opera Paediatrica.** R. Academiae Carolinae, Medico Chirurgicae Holmensis. I. Jundell, A. Lichtenstein, and A. Wallgren, Uppsala, 1945, pp. 629.

A volume of approximately fifty contributions by Swedish pediatricians commemorating 100 years of the pediatric clinic of the Caroline medical school. In 1845, Fredrik Th. Berg became the first professor of pediatrics in any medical school in the world, and started a course of instruction at the Caroline institute which placed pediatrics in Sweden on the same footing as the other branches of medicine. Lichtenstein contributes an interesting first article on the history of pediatrics in Sweden, and properly gives credit to Rosen von Rosenstein as being the "father of pediatrics" and the real founder of pediatrics as a science. Wallgren contributes an essay on "Social Welfare of Swedish Children" and Jundell discusses the pediatric clinics of the universities as centers of medical and medicosocial pediatric care, research, and instruction. These excellent introductory chapters are followed by some forty odd contributions by Swedish pediatricians. They cover nearly every phase of pediatrics and medical

research. It is interesting to note that 90 per cent of the articles are written in English, which in itself is a matter of historical interest. It is a dignified commemorative volume, giving the picture of the extent and development of pediatrics in Sweden of which our colleagues may well be proud. (The contributions were also published in *Acta Paediatrica*, vol 23. Fasc 34.)

B. S. V.

**MUSCLE TESTING** Techniques of Manual Examination. Lucille Daniels, Marian Williams, and Catherine Worthingham, Philadelphia, 1946, The W. B. Saunders Company, 189 pages. Price \$2.50

Following the acute state of poliomyelitis the physician in charge is naturally apprehensive regarding the prognosis and more specifically, the degree of muscle disability which may eventually ensue. To measure the improvement or lack of it, it has become the custom to institute at an early date a system of muscle testing.

Lovett in 1916 was the first to devise such a system of measurement, and it has stood the test of time remarkably well. However, during the last several years the incidence of polio has increased markedly and with it methods of treatment. It was but natural that the Lovett system of muscle testing should also be modified.

The authors of this little volume have done this in an extremely satisfactory manner. On the left page is an illustration of the relation of a muscle to be tested, its origin and insertion, with a brief discussion of the action of that muscle. On the opposite page is an illustration of the same muscle being tested on a patient. One is a complement of the other, and the effect of this method of presentation is extremely effective.

Those who are called upon to treat muscle deficiency of any kind, who wish to measure progress, or lack of it, will find this manual most helpful.

A pediatrician may not wish to do the actual testing of muscles but with the aid of this manual he will be able to more intelligently discuss his patient with the physical therapist called upon to do the muscle testing.

F. H. E.

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## Original Communications

### RHEUMATIC PNEUMONIA

#### REPORT OF TWO CASES

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THAT rheumatic disease is the result of reaction to foreign antigens is a possibility that has been investigated for a number of years, and evidence for the anaphylactic genesis of the exudative lesions is steadily accumulating. Rich and Gregory<sup>1</sup> stated in 1943 that an allergic arthritis indistinguishable from rheumatic arthritis may occur in serum sickness, that the lesions in sulfonamide anaphylactic pneumonitis are histologically identical to those of rheumatic pneumonitis, and that the sharply focal lesions of periarteritis nodosa can be duplicated by injections of foreign antigen. The same authors, in a later paper,<sup>2</sup> say that egg albumen and horse serum, used as sensitizing agents, produce pulmonary lesions in rabbits similar to those seen in sulfonamide hypersensitivity and rheumatic fever. It has long been suspected that the specificity of the rheumatic response is dependent not so much upon the infecting organism as upon the individual mechanism of the rheumatic subject. A focus of infection in such an individual produces sensitivity rather than immunity of cells in other parts of the body. Analogously, in experimental animals, implants of *Streptococcus hemolyticus* result in a condition of allergy and extreme sensitization of cells far removed from the site of the organisms. If minute doses of antigen are injected into the sensitized animal, an allergic reaction ensues which is manifested by severe, generalized edema.<sup>3</sup>

In addition to causing cellular sensitization, foreign antigens cause also the production of antibodies. If antigen and antibody meet in vascular tissue, the resulting reaction injures the previously sensitized endothelial cell of the capillary.<sup>2</sup> This mechanism could readily explain the recurrences of exudative features such as arthritic edema in persons with proliferative rheumatic lesions.<sup>3-5</sup> It may be also that streptococci render cardiac tissue antigenic in much the same way that they render kidney tissue antigenic in scarlet fever. Cavelti and Cavelti<sup>6</sup> have demonstrated in laboratory animals that the antigen (streptococci plus kidney tissue) causes the formation of autoantibodies which react with the antigen in renal capillary tufts to produce glomerulonephritis.

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Many investigators are of the opinion that the exudative lesions in rheumatic fever are likewise produced by this type of response to *Str. hemolyticus* infection.<sup>3</sup>

Pulmonic lesions in sulfonamide hypersensitivity, in anaphylaxis due to parenteral administration of foreign proteins, and perhaps in rheumatic fever, are due to focal endothelial cell injury with consequent increase in capillary permeability and transudation of albuminous fluid into the alveoli, alveolar ducts, alveolar septa, and interlobular spaces.<sup>3-7</sup> There is blood engorgement of the weakened alveolar capillaries, diapedesis of red blood cells into the alveoli, and infiltration of leucocytes into the alveoli and alveolar walls.<sup>19</sup> A severe anaphylactic reaction is seen in the cells of the septal wall as a focal cytoplasmic swelling with nuclear pyknosis and fragmentation. Necrosed septal walls rupture with resulting alveolar coalescence and intra-alveolar hemorrhage. If the endothelium of arterioles be damaged there is fibrinoid swelling of the arteriolar wall with polymorphonuclear and lymphocytic infiltration. This focal arteriolitis resembles the lesions of periarteritis nodosa.<sup>1</sup> Fibrinous and hyaline thrombi plug the ends of the ruptured vessels. The original albuminous transudate is pressed against the alveolar wall and, due to inspissation or to intra-alveolar air tension, becomes a hyaline membrane lining the alveoli and bronchioles.<sup>5</sup> Septal cells, or possibly the basal cells of bronchiolar epithelium,<sup>8</sup> proliferate to form a cellular lining of the alveolus and of the space formed by coalesced alveoli. These cells, assuming cuboidal shape, may form a single layer or they may be piled one on the other as a stratified cellular lining.<sup>9</sup> Many of them may contain hematogenic pigment. The plugs of fibrinous exudate which fill the alveolar ducts and project into alveolar spaces become organized and at first appear granulomatous, containing large spindle cells, mononucleated cells with abundant, pink-staining cytoplasm, pigmented macrophages, lymphocytes, and occasional erythrocytes. As organization proceeds, the plugs become fibrillary, with fibrin and fibroblasts arranged in layers like an onion. If the plug projects into and fills an alveolus lined with cuboidal cells, it appears to be covered by this layer of cells.<sup>10</sup> The completely organized plug consists only of dense fibrous tissue and may remain unchanged for an indefinite period, just as a healed Aschoff nodule may remain as a scar in the myocardium.<sup>9</sup> These plugs of organized exudate, sometimes called "Masson bodies," are probably cast or given specific shape by whatever mold, alveolar or ductal, that they happen to be in. There are often amorphous masses of organized exudate lying near by, which in no way differ from the Masson body in structural composition.<sup>10</sup> The pedicles of these plugs are attached to ductal or to septal walls and no doubt represent the route of invading fibroblasts in the process of organization. However, these plugs do not appear to connect with one another through the intra-alveolar pores as do the particles of organizing exudate in lobar pneumonia.<sup>9</sup> These peculiar, fibrous bodies are said to be present in bronchiectasis, tuberculosis, pulmonary abscess, and many other conditions in which focal intra-alveolar organization of blood or inspissated fibrin takes place.<sup>10</sup> Neubuerger and associates<sup>9</sup> view these Masson bodies, in part, at least, as granulomas

sprouting from the alveolar ducts, and the cuboidal alveolar lining as proliferated septal cells; whereas Herbut and Manges<sup>10</sup> and Herbut<sup>8</sup> insist that the bodies are organized, nonspecific exudate, and that the cuboidal cells are merely proliferated basal cells of the bronchiolar epithelium.

Since acute rheumatic fever is predominantly a childhood disease, and because most of the heart disease in children is rheumatic,<sup>2</sup> the possibility must be considered that the pneumonia which occasionally develops in a child with endocarditis is also rheumatic in origin.<sup>11</sup> Jensen<sup>12</sup> points out that probably many of the "primary atypical pneumonias" that have formerly been observed in cases of rheumatic fever were in reality rheumatic or poststreptococcic pneumonitis. Two cases of "atypical" pneumonia developing in the course of rheumatic fever are herewith presented.

#### CASE REPORTS

CASE 1.—A 7-year-old white girl, previously discharged from the Colorado General Hospital on Oct. 24, 1945, with a diagnosis of rheumatic heart disease, was readmitted, Jan. 17, 1946, with tachypnea and acute, postprandial, epigastric pain. There was no definite history of previous streptococcus infection. The patient was pale and apprehensive. Pulsations over the jugular veins were visible and palpable in the suprasternal notch, and a cardiac thrill was easily felt on the precordium. Heart rhythm was regular. A diastolic murmur was heard at the apex, and a mitral systolic soufflé was transmitted to the left axilla. The red blood cell count was 4,270,000, the hemoglobin was 9.6 Gm. per cent, and the sedimentation rate was 57 mm. in sixty minutes with hemocrit reading of 34 (Wintrobe). Platelet count, blood nonprotein nitrogen, plasma carbon-dioxide combining power, and urine were normal. Nose and throat cultures for *Str. hemolyticus* were negative. X-ray films of the chest showed congestive changes in both lungs and bilateral enlargement of the heart with the transverse diameter 2.5 cm. greater than on the previous admission. Electrocardiograms showed left ventricular strain. Despite absolute bed rest, high-vitamin, high-caloric diet, continuous oxygen inhalation, multiple blood transfusions, diuretic therapy, and digitalization, the clinical course was steadily downward to final expiration three weeks after admission.

*Autopsy.*—The autopsy was made seventeen hours after death. The unopened pericardial sac measured 14 cm. in diameter transversely, 13 cm. longitudinally, and 14 cm. obliquely through the apex. It was distended with 500 c.c. of fibrinous, straw-colored fluid with most of the fibrin settled posteriorly. The heart weighed 220 grams (twice average normal weight) and was pale and flabby. The epicardium was dull and covered with a thin film of fibrin. The thickened myocardium was pale but otherwise normal grossly. The endocardium was thick and wrinkled in the left auricle. Tricuspid, mitral, and aortic valvular cusps were opaque and showed numerous tiny, red, verrucose nodules on their apposing surfaces near the margins. The pulmonic cusps and all valve circumferences were normal. The left lung weighed 300 grams, the right, 430 grams (approximately three times average normal weight). They were mottled, bluish-purple, firm posteriorly, and irregularly crepitant anteriorly with slight elevation of the pink-yellow, crepitant areas above the surface of the firm portions. Multiple sections were flat and firm with very wet, dark red surfaces. The bronchial mucosa was hyperemic and the lumens contained frothy, blood-tinged fluid. Other organs appeared normal.

*Microscopic examination.*—The epicardium was thick with fibrous tissue, had a rough, fibrinous surface, and showed numerous small areas of fibrinoid degeneration invested by large mononuclear and multinuclear cells, which were in turn surrounded by lymphocytes and polymorphonuclears. In some places, fibroblastic proliferation was pronounced and collagen fibrils were very dense. Those subepicardial muscle fibers which were in contact with



the epicardial Aschoff body had either been replaced by connective tissue or showed cytoplasmic swelling and granulation with nuclear rhexis, pyknosis, or dissolution. The myocardium contained numerous Aschoff nodules. The lesions were focal, apparently in the arterial adventitia, and in the active phase of their production. There was no scarring, very little central necrosis of the nodule, and quite pronounced leucocytic infiltration. The endocardium (valvular cusps) was thick, fibrous, and contained lymphocytes, polymorphonuclear leucocytes, and diffusely scattered Aschoff cells that had made a slight attempt at palisading along the contact margin of the cusps. On some of the endocardial nodules there were degenerated masses of collagen, some of which pressed into the nodule while others appeared about to break away. Organisms could not be demonstrated.

The pleura was thickened with fibrous tissue and infiltrated mildly with lymphocytes. Alveolar walls were thick with proliferated septal cells and showed some hyalinization. In many places the wall projected as a knob of cells into the alveolus. Many alveolar walls showed necrosis and rupture with alveolar coalescence. The ruptured walls appeared to have contracted and presented bulbous ends plugged with pink-staining, collagenous material. Many alveoli were lined partially or completely with a single row of fusiform and cuboidal cells. These cells, slightly larger than lymphocytes, had definite fibrillary processes. Some of them contained particles of brown pigment. Apparently, the same cell became rounder, larger, and more burdened with pigment as it approached the center of the alveolus. Some alveoli contained blood and edema fluid; nearly all of them were packed with large, pigment-laden macrophages. Arteries in many places showed pronounced thickening of the adventitia on one side. In the center of this thickening was a cluster of large cells of the epithelioid type, some multinuclear, resembling Aschoff cells of the heart. Epithelium of the bronchi and bronchioles was normal.

The cortex and medulla of the cerebrum showed occasional, small, paravascular collections of lymphocytes.

Nothing remarkable was observed in other organs.

CASE 2.—A 9-year-old white boy was admitted to the Colorado General Hospital, Nov. 23, 1945, because of fever, anorexia, severe joint pains, and stabbing pains in the heart region. He first had these symptoms three weeks after a severe attack of scarlet fever in 1942, and since that time had had similar attacks nearly every month except during the summer. Between these episodes he had been symptom free. The boy was pale and undernourished. The pharynx was injected posteriorly, and cervical lymph nodes were enlarged. Examination of the heart elicited a precordial thrill, a loud systolic murmur, and a middiastolic murmur heard best at the apex. Hemoglobin was 12 Gm. per cent; the white blood count was 13,000 with 66 per cent polymorphonuclears. Urine was normal. Nose and throat cultures were negative for *Str. hemolyticus*. The patient was placed on absolute bed rest and supportive therapy. Signs of pulmonary disease developed. X-ray revealed heart enlargement and an extensive, mottled density of the right lung. Electrocardiograms showed slight right axis deviation. Continuous oxygen inhalation, intermittent penicillin and sulfadiazine administration, salicylization, and digitalization proved of no avail. Cardiac and pulmonary embarrassment progressed, anasarca developed, and the patient died three weeks after admission.

*Autopsy.*—The autopsy was performed nine hours after death. The peritoneum was smooth, glistening and contained 800 c.c. of clear amber fluid. The pericardium had a smooth, rather dull lining and contained 40 c.c. of fibrinous fluid. The heart weighed 290 grams (two and one-half times average normal), showed a dull epicardial surface, a pale, thick myocardium, and slightly shortened mitral cusps that had a row of firmly attached, pinhead-sized nodules on their apposing surfaces near the margins. The aortic valves were opaque but normal otherwise. Valve circumferences were within normal limits. The right lung weighed 470 grams (two and one-half times average normal), had a finely mottled surface, a purple-red color, a granularly firm consistence, and a peculiar, cut-surface mottling throughout. The firm, red areas appeared as small islands in the section surfaces. The left lung weighed 480 grams and presented gross features similar to those of the right lung.

Frothy, hemorrhagic fluid exuded from both bronchi. The brain, weighing 1,470 grams, showed mild edema, some leptomeningeal hyperemia, and slightly dilated ventricles full of clear fluid. Other organs appeared normal.

*Microscopic examination.*—Epicardial vessels were congested, and fibrous tissue was greatly increased. Subepicardial muscle cells were vacuolated. Many fibers were atrophied, and some were replaced with connective tissue which was abundant throughout. A few fibrosed, fusiform, Aschoff nodules dotted the myocardium. The endocardium was thick, fibrous, highly vascular, and contained collections of large, multinuclear cells. The bases of the mitral cusps were marked by extensive fibrosis, leucocytic infiltration (lymphocytes predominating), slight palisading of the Aschoff cells, interfibrillar vacuolization, and fibrin deposition on the surface.

The pleura was slightly thickened with fibrous connective tissue. Some alveoli were partially collapsed; some showed dilatation; others showed septum necrosis with rupture and alveolar coalescence. In some areas the alveoli were filled with blood and large vacuolated mononuclears, in others with mononuclears, lymphocytes, and polymorphonuclears, in still others with pigment-laden macrophages, polymorphonuclears, and edema fluid. Some of the alveolar walls were lined with hyaline membranes; others were thick and partially lined with several layers of septal cells. Emphysematous areas roughly alternated with areas of alveolar collapse and blood engorgement. Scattered throughout the lungs were variously shaped bundles of fibrous tissue which projected into alveoli from alveolar ducts. Cross sections of these bundles were, in the main, oval, round, or fusiform, and showed pronounced cellular polarity and whorl arrangement. Some were hollow and contained blood.

The meninges were thickened with fibrous tissue and contained small areas of necrosis partially surrounded by large flattened mononuclears, lymphocytes, plasma cells, and polymorphonuclear leucocytes. Arterial walls showed focal thickening and fibrosis with leucocytic infiltration and apparent vascularization in some places. Small, intracortical arteries showed adventitial thickening and tiny areas of fibrinoid degeneration surrounded by lymphocytes and large cells with abundant cytoplasm. Neuronal changes could not be demonstrated.

#### COMMENT

Some of the recent literature presents evidence which militates against rheumatic pneumonia as a disease entity. Much of it, however, not only supports the view that the pulmonary lesions are specific but also that they are allergic in their genesis and manifestations. By some investigators the Masson body is interpreted as an organized, nonspecific exudate; by others it is looked upon as a definite granuloma equivalent to the Aschoff body of the rheumatic heart.

According to the theory of allergenesis of exudative rheumatic pneumonitis, the antigens fabricated in the proliferative lesions of the heart circulate and sensitize cells of the pulmonary alveolar endothelium, and, in addition, bring about a gradual increase in humoral antibodies. When antibody titer is sufficiently high, the antigen-antibody reaction becomes violent enough to injure the sensitized cells. Resulting exudative lesions (as in the two cases reported) are seen in all phases of their production from slightly increased capillary permeability with edema, through endothelial necrosis and hemorrhage, to organization of the exudate and final fibrosis. In the first case, active proliferative lesions existed only in the heart. Exudative lesions were in the early active phase in the lungs and probably just beginning in the brain; death occurred before healing could begin. In the second case, proliferative lesions

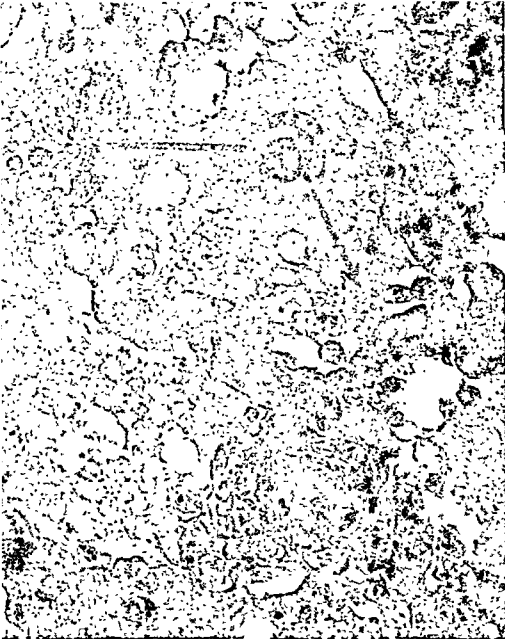


Fig. 1.

Fig. 1.—Section of lung (Case 1) showing septal wall congestion, alveolar transudate, and red blood cell diapedesis (a).  $\times 450$ .

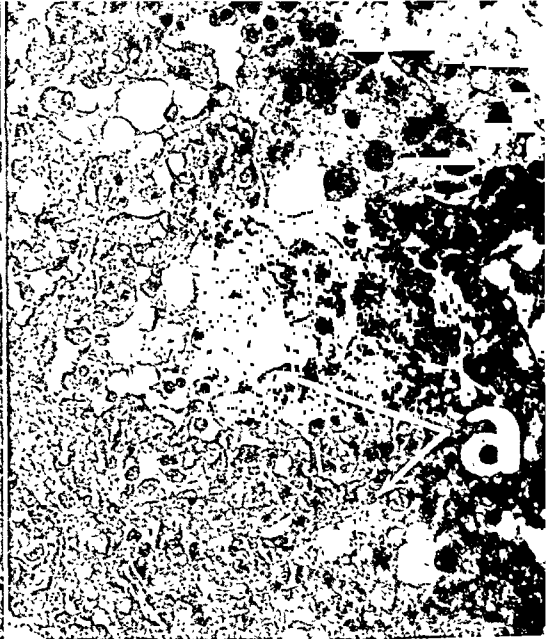


Fig. 2.

Fig. 2.—Section of lung (Case 1) showing septal cell proliferation and thickening of the alveolar wall (a).  $\times 350$ .



Fig. 3.

Fig. 3.—Section of lung (Case 1) showing mitotic figure in proliferating septal cell (a).  $\times 970$ .

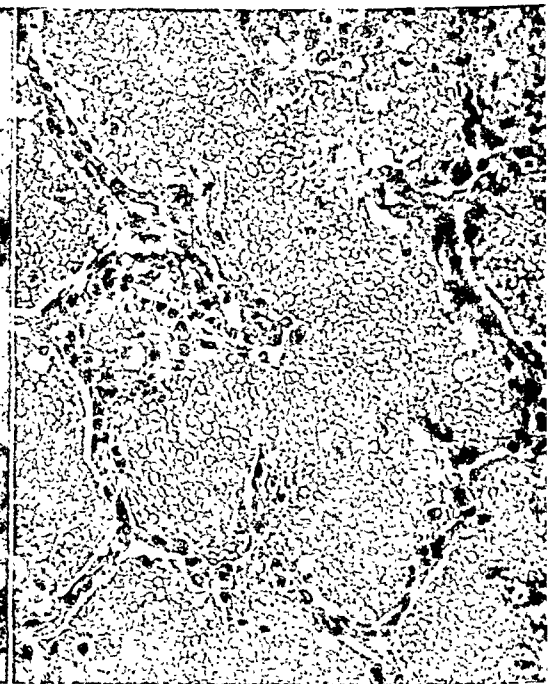


Fig. 4.

Fig. 4.—Section of lung (Case 1) showing rupture and collapse of septal walls with alveolar coalescence and hemorrhage.  $\times 200$ .

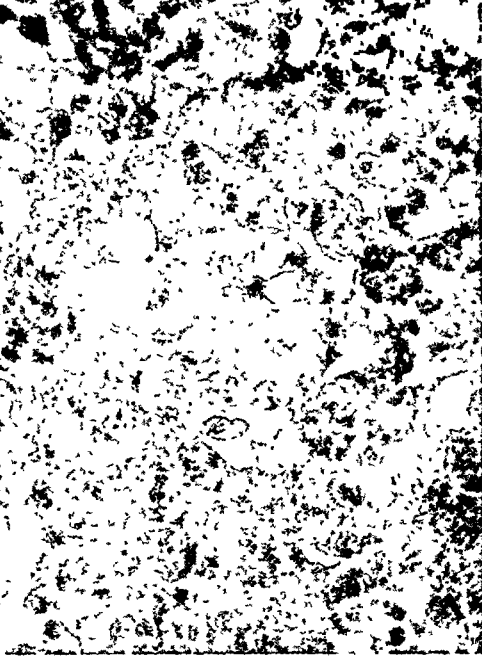


Fig. 5.

Fig. 5—Section of lung (Case 1) showing partial lining of alveolus with a single layer of cuboidal cells. X450.

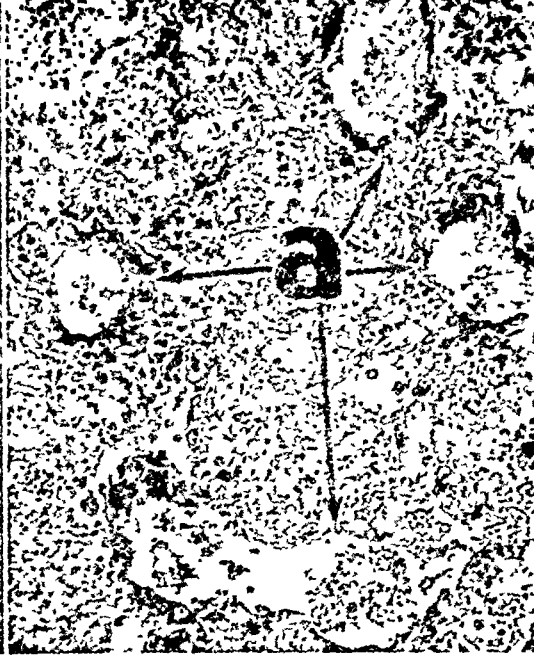


Fig. 6.

Fig. 6—Section of lung (Case 1) showing several alveoli lined with hyaline membranes (a). X150.

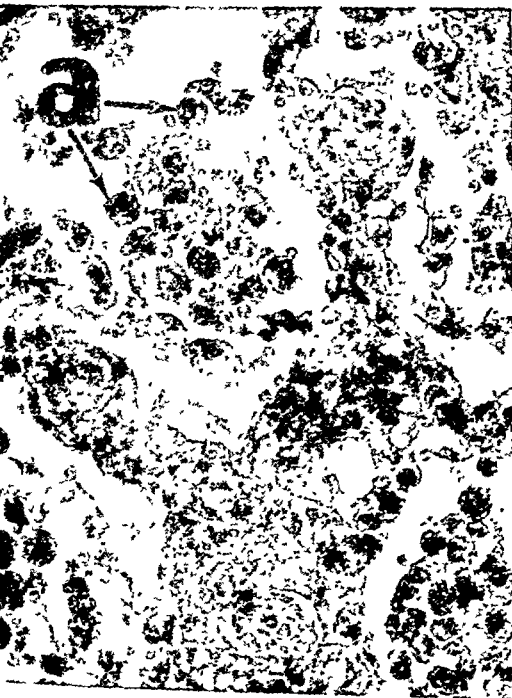


Fig. 7.

Fig. 7—Section of lung (Case 2) showing fibrinous plugs in ends of ruptured septa and alveolar infiltration with pigmented macrophages (a). X450.

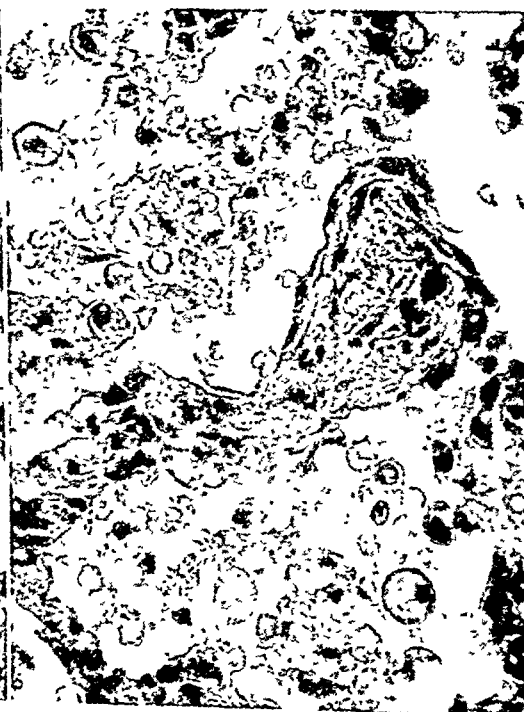


Fig. 8.

Fig. 8—Section of lung (Case 2) showing an incipient Masson body with early fibroblastic investment of a particle of exudate. X450.

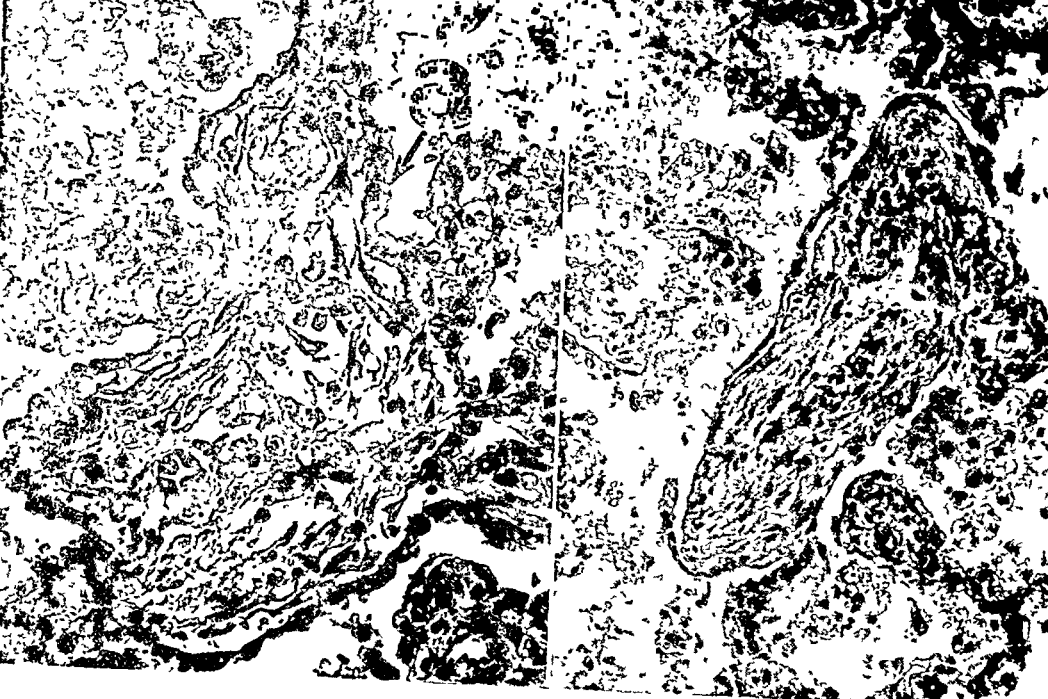


Fig. 9.

Fig. 10.

Fig. 9.—Section of lung (Case 2) showing a granulomatous Masson body surrounded by a single layer of cuboidal cells (a).  $\times 450$ .

Fig. 10.—Section of lung (Case 2) showing a fibrillary Masson body.  $\times 350$ .



Fig. 11.

Fig. 12.

Fig. 11.—Section of lung (Case 2) showing a Masson body with two septal attachments (pedicles) and pronounced cellular polarity and whorl arrangement.  $\times 350$ .

Fig. 12.—Section of lung (Case 2) showing a fibrous Masson body.  $\times 150$ .

of the heart were healing, exudative lesions of the lung and brain were clearing, and a few incipient proliferative lesions were appearing in adventitial connective tissue of the lung and brain.

The roster of supporters for the theory of specificity of rheumatic pulmonary lesions is increasing. Since Stoll<sup>14</sup> in 1788 spoke of rheumatic peripneumonia, others, including Garrod,<sup>15</sup> Paul,<sup>16</sup> Naish,<sup>17</sup> Masson and co-workers,<sup>18</sup> and Neuburger and associates,<sup>9</sup> have accumulated evidence for such specificity. If the specific pulmonary lesion is anaphylactic in nature, as recent evidence seems to indicate, then the method of therapeutic attack in rheumatic fever will be altered considerably. It is not unlikely that rheumatic fever immunization, either active or passive, can some day be produced in the human being—a hope that may stimulate further investigation in this field.

Figs. 1 to 12 are microphotographs of the pulmonary lesions of the two patients whose cases are presented. These pictures portray in chronologic sequence the pathologic changes as they are generally understood in the dim light of present available information.

#### SUMMARY

Two new cases of so-called rheumatic pneumonia are presented. Together, these two cases of lung affection in children with rheumatic heart disease show most of the features of an exudative lesion resulting from injury to capillary endothelium. Pulmonary histopathology parallels that seen in experimental and sulfonamide anaphylactic pneumonitis.

The clinical histories of the two patients reported are consistent with the concept of an allergic mechanism in the production of pulmonary pathology and lay stress on the point that an exudative reaction such as pneumonitis may be delayed for some time after symptomatic subsidence of the initial endocarditis. This thought must be borne in mind in all cases of sulfonamide-penicillin-resistant pneumonia occurring in children with histories of rheumatic fever.

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# HISTOPLASMOSIS IN INFANCY

REPORT OF A CASE IN AN INFANT, WITH A BRIEF CLINICOPATHOLOGIC REVIEW

ALEXANDER M. IAMS, M.D.,\* AND HADDOW M. KEITH, M.B. (TORONTO)†  
ROCHESTER, MINN.

IN 1906, Darling reported the first case of histoplasmosis, from the Panama Canal Zone. In this report and in his two succeeding reports in 1908 and 1909, he stated that he regarded the etiologic organism to be a protozoan similar to the genus *Leishmania*. It was not until 1921 that Rocha-Lima first suggested, and not until 1934 that de Monbreun definitely established that the organism is a fungus of the genus *Posadasia*. In tissues, the organism exists as a thick, encapsulated yeast cell, 1 to 5 microns in diameter. It is usually found in the large, mononuclear, reticuloendothelial cells.

Since Darling's first article, eighty-eight cases of histoplasmosis have been reported. In twenty-eight of these, the patients were children. Twenty were infants less than 15 months of age. Because in few of these cases was histoplasmosis diagnosed clinically and because the present case has some interesting features, a report in conjunction with a short review of the clinicopathologic picture in infants may be of value.

## CLINICOPATHOLOGIC REVIEW

Of the eighty-eight cases in the literature, the distribution has been world wide. The majority of the cases however, have come from the Mississippi River basin, where the disease is apparently endemic. As was stressed in an article by Iams and associates,<sup>1</sup> the clinical picture presented in infants is quite different from that in adults. As the case reported in this paper will illustrate, the usual clinical findings in an infant consist of fever, loss of weight, chronic cough, and diarrhea, associated with hepatosplenomegaly, lymphadenopathy, hypochromic normocytic anemia, and leucopenia. If a patient presents all of the findings in Group A, Table I and one or more of the findings in Group B, Table I, histoplasmosis should be considered a definite possibility.

TABLE I. CLINICAL FINDINGS IN HISTOPLASMOSIS OF INFANTS\*

GROUP A	GROUP B
Fever and loss of weight	Leucopenia or normal leucocyte count
Hypochromic normocytic anemia	Lower respiratory infection
Splenomegaly	Gastroenteritis
Hepatomegaly	Lymphadenopathy
	Dermatitis
	Upper respiratory infection

\*Arranged in order of frequency in twenty reported cases.

Pathologically, the fungus involves, in order of frequency, the lungs, lymph nodes, liver, spleen, gastrointestinal tract, bone marrow, adrenal glands, thymus, skin, pancreas, myocardium, kidneys, and brain (Table II).

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	Upper respiratory infection

\*Arranged in order of frequency in twenty reported cases.

Pathologically, the fungus involves, in order of frequency, the lungs, lymph nodes, liver, spleen, gastrointestinal tract, bone marrow, adrenal glands, thymus, skin, pancreas, myocardium, kidneys, and brain (Table II).

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TABLE II. SITES OF PATHOLOGIC FINDINGS IN HISTOPLASMOSIS OF INFANTS\*

GROUP A	GROUP B
Lungs	Bone marrow
Lymph nodes	Adrenal glands
Liver	Thymus
Spleen	Skin, pancreas, myocardium, etc.
Gastrointestinal tract	

\*Arranged in order of frequency in twenty reported cases.

*Diagnosis.*—In infants and children as well as in adults, there are several disease processes with which histoplasmosis might be confused. Because of the hepatosplenomegaly and lymphadenopathy, the lymphoblastomatous diseases must be ruled out. These diseases might present all of the clinical findings in Group A and several of the clinical findings of Group B (Table I) and thereby satisfy the requirements for a clinical suspicion of histoplasmosis. Blood studies and biopsy of a lymph node or bone marrow will usually show the characteristic pathologic pictures of these diseases.

In cases of tuberculosis, all or most of the clinical findings of Group A and part of Group B might also be present. The roentgenographic findings in the thorax in the two diseases are quite similar and may further confuse the picture. The diagnosis could best be made by the diagnostic methods used in tuberculosis or by sternal biopsy.

Pancreatic cystic fibrosis might also offer some difficulties in differentiation. Chronic cough, loss of weight, anemia, diarrhea, and fever are observed in both diseases. Also, the roentgenologic findings might be quite similar. However, hepatosplenomegaly is not commonly observed in pancreatic fibrosis. The diagnostic laboratory studies used in each of these diseases are adequate to enable one to make a final decision.

Erythroblastosis foetalis and congenital syphilis may present some of the clinical findings of histoplasmosis. Blood Wassermann reactions and Rh factor studies of the parents and infant will usually serve to differentiate these diseases.

The diagnostic procedures used in histoplasmosis are biopsy of bone marrow, liver, and spleen, thick blood smears, blood cultures, and intradermal tests with histoplasmin.<sup>2</sup> The most dependable of these methods is biopsy of the bone marrow or one of the organs.

*Prognosis.*—The prognosis as far as has been determined at the present time is uniformly poor. In all but one case reported to date the patient has died.

#### CASE REPORT

The patient, a female infant, was born in Illinois on April 7, 1945, after a full forty weeks' gestation. Her mother, thirty-five years of age, father, forty-one years of age, and a sibling, three years of age, are all living and in good health. The infant weighed 7 pounds, 8 ounces (3.40 kilogram) at birth, gained well on formula feedings, and was in normal health until June, 1945. At the age of 2 months she was seen by the family physician because of fussiness, irritability, and sleeplessness. She was found to be moderately anemic and responded well to iron therapy.

The infant remained apparently well until October, 1945, when, at 6 months of age, she was again taken to her family physician because of icterus, pallor, and a temperature of 103° F. At this time hepatomegaly was first noted and a diagnosis of hepatitis was made.

Her general condition became worse and on November 9, râles and decreased breath sounds were noted on the left side of the thorax posteriorly. A large spleen was also found. The concentration of hemoglobin was 7.5 Gm. per 100 c.c. of blood; erythrocytes numbered 2,760,000 and leucocytes 3,900 per cubic millimeter of blood, with lymphocytes 41 per cent and polymorphonuclears 59 per cent. The cerebrospinal fluid showed three lymphocytes but was otherwise negative. A roentgenogram of the thorax was negative. The patient's temperature continued elevated between 103° and 104° F. A diagnosis of atypical pneumonia with associated aplastic anemia was made and the patient was treated with whole blood transfusions, sulfonamides, and penicillin.

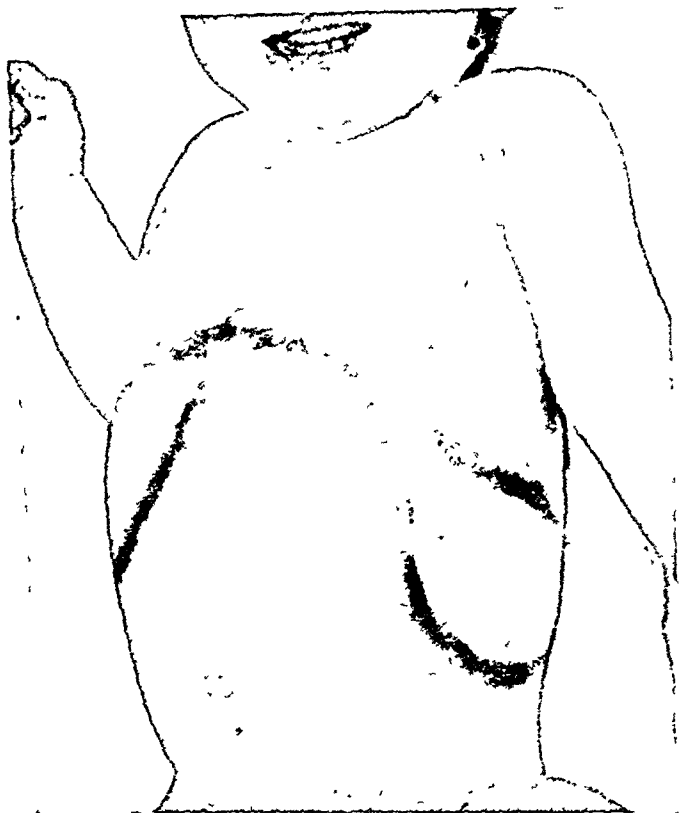


Fig. 1.—Infant with liver and spleen demarcated.

On Nov. 13, 1945, at the age of 7 months, the patient was referred to the Mayo Clinic and was admitted to a hospital for further study and treatment.

The physical examination on admission to the hospital showed a well-nourished, well-developed, moderately pale infant, appearing chronically ill. Her rectal temperature was 101.5° F. The liver and spleen were enlarged five centimeters below the costal margins (Fig. 1). There were no other abnormal physical findings. She weighed 18 pounds (8.15 kilograms).

At this time the concentration of hemoglobin was 12.6 Gm. per 100 c.c. of blood; erythrocytes numbered 3,640,000 and leucocytes, 1,900 per cubic millimeter of blood. Urinalysis showed no abnormalities. There was no increased fragility of the erythrocytes. No plasmodia were found in a thick smear. Blood smears showed hypochromic, macrocytic anemia with increased regeneration, occasional basophilic stippling, and toxic granules in the polymorphonuclear cells. The flocculation reaction for syphilis was negative. The concentra-

tion of the serum bilirubin both direct and indirect was within the normal range. The sulfobromophthalein liver function test showed retention of the dye, grade 1 (on the basis of 1 to 4, in which 1 designates the least and 4 the greatest retention). The cephalin flocculation reaction was positive. The prothrombin time (Quick's test) was 19 seconds (normal). The concentration of proteins was 5.8 Gm. per 100 c.c. of serum with an albumin-globulin ratio of 3.06:1. Roentgenograms of the thorax, head, and long bones were all normal. Blood cultures taken at this time were reported negative in forty-eight hours.

The patient's course was stormy during hospitalization. The rectal temperature curve ranged from 99.6° to 104.0° F. each day, with peaks at 8:00 A.M. and 8:00 P.M. This type of curve persisted until she died. She lost weight rapidly, and on November 19, weighed 7.62 kilograms, 0.53 kilogram less than on admission.

On November 22, administration of 10,000 units of penicillin every three hours was begun. This was continued for only eighty-four hours, the patient having received 240,000 units in all. Penicillin was of no apparent value to the patient. At this time, the concentration of hemoglobin was 8.25 Gm. per 100 c.c. of blood; erythrocytes numbered 2,710,000, and leucocytes 1,100 per cubic millimeter of blood. Numerous differential counts of the leucocytes revealed neutrocytosis with a shift to the left. Seven transfusions of citrated whole blood (60 to 75 c.c. each) were given on alternate days. However, they were of only momentary value, for the profound anemia became even more severe. On December 10, laboratory studies showed 2,150,000 erythrocytes per cubic millimeter of blood and 7.3 Gm. of hemoglobin per 100 c.c. of blood.

Because of the history, physical findings, hypochromia, macrocytic anemia, and leucopenia, histoplasmosis was suspected, and a biopsy of bone marrow was done on Nov. 23, 1945, by Dr. Hargraves of the Division of Medicine, Mayo Clinic. His report is as follows:

"A satisfactory bone marrow preparation was obtained by tibial puncture. There were some units present. Smears were made in the usual fashion and stained with Wright's stain. Examination of the smears showed moderate cellularity present with the usual myeloid-erythroid ratio. There were some basophilic normoblasts and pronormoblasts but most of the normoblasts were late polychromatophilic cells. In the myeloid line there were numerous older forms with about a normal age dispersion of the immature forms. Most of the mature neutrophils were vacuolated and appeared to be degenerating forms. In the cytoplasmic vacuoles of many of these cells were inclusion bodies about the size of platelets, many showed a sharply defined capsule and there was a central mass of chromatin which was rather smooth and dark.

"An occasional monocyte was found with multiple organisms in a large vacuole. There were many large phagocytic reticuloendothelial cells with these same organisms contained in their cytoplasm—some having as many as twenty present. One eosinophile was seen containing two parasites, and an occasional megakaryocyte was also parasitized. Interestingly enough, I was unable to find them in any of the immature forms, either myeloid or erythroid, and no lymphocytes were seen parasitized. This would suggest that the parasites were phagocytized by the mature cells. There were many free organisms found around clumps of cells and strung out alone in some fields. These were undoubtedly *Histoplasma capsulatum* (Histoplasmosis of Darling)." Figs. 2 to 6 show the organism.

At this time, histoplasmin dermal tests were applied to both of the infant's forearms in dilutions of 1:1,000, 1:500, 1:100, and 1:10, with proper controls, and the tests were repeated three days later, with no reaction in forty-eight or seventy-two hours. A dermal test was also applied to the forearm of the patient's mother. In forty-eight hours the erythematous area of the histoplasmin test on the patient's mother measured 5.4 by 3.6 cm. The erythematous area of the control reaction measured 2.4 by 1.6 cm. This was considered a positive reaction.

Soon after the diagnosis of histoplasmosis had been made by means of the bone marrow biopsy, specific treatment was attempted. To date, the only specific therapeutic agent mentioned in the literature is Neostam (nitrogen glucosides of sodium paraminophenyl stibonate). This was given intramuscularly to the patient in doses of 0.001 Gm. per pound of body

Fig. 2.



Fig. 3.



Fig. 4.

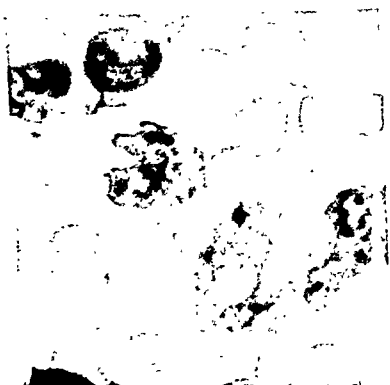


Fig. 5.

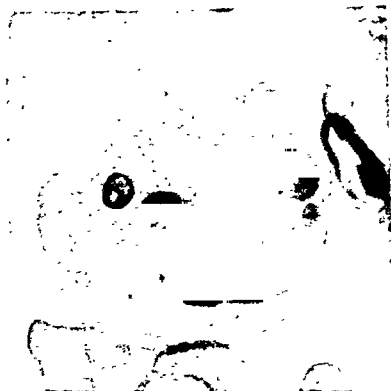


Fig. 2.—Bone marrow showing *Histoplasma capsulatum* in a reticulo-endothelial cell (Wright's stain,  $\times 1,000$ ; section made by Dr. M. M. Hargraves).

Fig. 3.—Organisms in monocyte (Wright's stain,  $\times 1,000$ ; section made by Dr. M. M. Hargraves).

Fig. 4.—Organisms in polymorphonuclear leucocyte (Wright's stain,  $\times 1,000$ ; section made by Dr. M. M. Hargraves).

Fig. 5.—Organisms in megakaryocyte (Wright's stain,  $\times 1,000$ ; section made by Dr. M. M. Hargraves).

Fig. 6.—Organisms in eosinophile (Wright's stain,  $\times 1,000$ ; section made by Dr. M. M. Hargraves).

Fig. 6.





weight, amounting to 0.01 Gm. per day on December 12 and 14. This seemed to have no influence one way or another. The blood cultures that had been taken previously were reported in ten days as showing many colonies of *Histoplasma capsulatum*. Cultures of the sternal marrow also gave positive results. Stools were cultured on plates of hormone blood agar with 20 units of streptomycin added as described by Thompson,<sup>2</sup> and colonies of *Histoplasma capsulatum* grew out. Secretions from the duodenum were obtained by tube and cultured at room temperature in like manner and also showed growth of *Histoplasma capsulatum* in twenty days. Repeated cultures of the urine were all negative.

The infant's condition became progressively worse. Tube feeding was necessary for the last two weeks of the patient's life because of anorexia and weakness. On December 15, she became very listless, cyanotic, and dyspneic, and petechial hemorrhages appeared on the trunk. She was placed in an oxygen tent. The following day edema of the lower extremities were first noted. She began vomiting all her feedings, respirations became more rapid, and she died.

Because of the positive reaction to the histoplasmin dermal test, the patient's mother was examined for any signs of latent histoplasmosis. Physical examination was entirely negative with the exception of two involuting macules on the right breast which represented previous draining pustules. The concentration of hemoglobin was 13.5 Gm. per 100 c.c. of blood; erythrocytes numbered 4,220,000 and leucocytes 9,000 per cubic millimeter of blood, with lymphocytes 29 per cent, monocytes 3, polymorphonuclears 66, eosinophiles 1, and basophiles 1 per cent. The flocculation reaction for syphilis was negative. The erythrocyte sedimentation rate (Westergren) was 28 mm. per hour. A roentgenogram of the thorax was normal. No signs of histoplasmosis could be found.

**Necropsy.**—Necropsy revealed the typical pathologic picture of the disease. The heart, lungs, liver, spleen, kidneys, adrenals, esophagus, large bowel, urinary bladder, lymph nodes, thymus, bone marrow, and diaphragm, were all found to be invaded by the organism.

The organism was cultured from the blood, lungs, liver, spleen, kidneys, bone marrow, rectus abdominis muscle, and frontal lobe of the brain.

The pathologic and bacteriologic findings will be published in full elsewhere.<sup>4</sup>

#### COMMENT

There are several interesting factors in this case. It is one of the few cases in the literature in which the diagnosis was made ante mortem. This was accomplished primarily by considering the disease as a possibility because of the clinical picture. This led to a biopsy of bone marrow revealing the organism.

In our case, the organism was cultured for the first time from the stools, duodenal drainage, and urine. This gives evidence of the infectiousness of histoplasmosis and adds some facts to the still vague epidemiological picture of the disease.

The reactions to the intradermal tests were particularly interesting but definite interpretation is lacking. The negative reaction of the infant duplicates previous experience at the Mayo Clinic in an unreported case. This reaction may be considered comparable to that seen with tuberculin in miliary tuberculosis. This, however, is not the experience of several authors in the literature.<sup>5-7</sup> The positive reaction of the patient's mother, with no evidence of histoplasmosis, is interesting but also without any adequate explanation. One might postulate the presence of a previous or latent infection with a possible intrauterine invasion of the infant. However, Emmons and his associates<sup>8</sup> have shown the lack of specificity of the histoplasmin intradermal test in particular and fungus intradermal tests in general. They studied antigens prepared from cultures of



*Histoplasma capsulatum*, *Blastomyces dermatitidis*, *Coccidioides immitis* and *Haplosporangium parvum*. Cross reactions were demonstrated between all four antigens. A positive reaction to 1:100 histoplasmin was shown in guinea pigs, experimentally infected separately with histoplasmosis, blastomycosis, coccidioidomycosis or haplomyecosis. Positive reactions were found in patients to both histoplasmin and blastomycin. The possibility of a latent, low-grade histoplasmosis, leaving the patients perfectly well but showing calcified hilar nodes and a positive histoplasmin intradermal reaction, has been postulated by Palmer.<sup>9</sup> The studies of Emmons and his associates cast a shadow of doubt on these postulations but further study is indicated.

#### SUMMARY

A case of histoplasmosis in an infant is reported, with a brief review of the clinical and pathologic picture. This report is distinctive in that the organism was cultured for the first time ante mortem from the stool, urine, and duodenal drainage.

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# SALICYLATE INTOXICATION IN THE INFANT AND YOUNG CHILD

## A REPORT OF THIRTEEN CASES

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**S**PORADIC cases of salicylate intoxication have been seen at the St. Louis Children's Hospital in the past.<sup>1</sup> During the period of October, 1944, to June, 1946, there were thirteen patients with salicylate intoxication admitted to the hospital. Most of these patients were infants who received aspirin as treatment for a "cold." In only two instances was accidental ingestion of medication reported. The danger of salicylate poisoning cannot be over-emphasized to parents or physicians who administer salicylate to children, and especially to infants. This danger obviously is intensified when salicylates are given over a period of several days or in large doses. Case reports in the literature of salicylate intoxication have increased during the past year. This report represents the largest group of patients with salicylate intoxication admitted for hospital care. A similar pattern of acid-base imbalance was noted in all of these patients, and this response is presented as that typical of salicylate intoxication in the infant and young child.

## METHODS

In each of the thirteen cases reported, studies included salicylate concentration of the blood plasma and spinal fluid,\* pH of the blood serum by the method of Hastings and Sendroy,<sup>2</sup> carbon dioxide content of the serum,<sup>4</sup> prothrombin time by the method of Ziffert and associates,<sup>5</sup> and urine examination. Other laboratory studies included serum chloride, glucose, and nonprotein nitrogen determinations. Blood ketone body studies<sup>6</sup> were made in two cases. A large vein was selected for venipuncture (usually the femoral vein), and the blood was obtained carefully in a chemically clean and sterile syringe, and placed immediately under paraffin oil so as to avoid changes in pH and carbon dioxide. Therapy was instituted immediately after the blood samples were taken because of the severe state of collapse noted in most of these patients. An attempt was made to determine the amount of salicylate administered to or accidentally ingested by the patient. In most instances, information was obtained by questioning the parents and the pharmacist filling the prescription.

## ANALYSIS OF CASES

*Age, Sex, and Race.*—The ages of the patients ranged from 3 weeks to 3½ years. There were six girls and seven boys; most of the younger patients were boys. All of the children were white except two Negro siblings.

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\*The method of Brodie and associates<sup>7</sup> was employed for these determinations, and the results were expressed in milligrams per 100 c.c. For comparison with other reports in the literature, 1.0 gamma per c.c. is equivalent to 0.1 mg. per 100 c.c.

TABLE I. SYMPTOMS AND SIGNS NOTED IN CASES OF SALICYLATE INTOXICATION

CASE	AGE	SALICYLATE RECEIVED	SYMPTOMS AND SIGNS	TEMPERATURE ON ADMISSION (°C.)	TOTAL WBC
1	3 wk.	22½ grains in 2 days (aspirin)	Cold with cough, 4 days (aspirin started 3½ days before entry); deep, pauseless breathing, 2½ days; attacks of cyanosis, 2 days (aspirin discontinued 24 hr. before entry); moderate dehydration	39.5	10,100
2	6 mo.	27 grains in 1 day (aspirin)	Deep, pauseless breathing, 24 hr. (beginning about time aspirin was started but increasing during that period); slight dehydration; listlessness; color of skin gray; pharynx reddened	38.5	9,150
3	26 mo.	15 grains in 2 days (aspirin)	Cough, 4 days (aspirin started 4 days before entry); vomiting, 3 days; deep, pauseless breathing, 2 days (aspirin discontinued 1½ days before entry); listlessness, 2 days; semistuporous on entry; moderate dehydration; acute rhinopharyngitis and bronchitis	38.5	12,800
4	8 mo.	Yellow pills (?) 8 daily for 4 days	Fever and cold 5 days ("yellow pills" started 4 days before entry); vomiting 2-3 days before entry (medication discontinued before entry); deep, pauseless, and rapid breathing, 24 hr.; listlessness, 24 hr.; slight dehydration and cyanosis; acute, serous otitis media, right; right sixth cranial nerve palsy; convulsions 1-3 days after entry to hospital	39.5	19,600
5	4½ mo.	60 grains in 3½ days (aspirin)	Cold, 1 week (aspirin started 3½ days before entry; fever, 3 days; anorexia and vomiting, 3 days; deep pauseless respiration, 1 day; stuporous, 4 hours; convulsive twitching, 3 hours; comatose on entry; moderate dehydration; rhinopharyngitis, bronchitis, acute catarrhal otitis media bilateral	40.0	11,300
6	3½ mo.	10-15 grains per day (mother vague and reluctant in giving dosage of aspirin)	Cold, 1 week (aspirin given frequently by mother, dosage vague, patient had at least 10-15 grains in 24 hr. prior to entry); deep, pauseless breathing 18 hr.; listlessness, 18 hr.; comatose on entry; skin ashen gray in color; moderate dehydration; acute rhinopharyngitis	38.5	17,000
7	2½ yr.	45 grains in 2 days (aspirin)	Cold, 5 days (aspirin begun 2 days before entry); deep, pauseless breathing, 12 hr.; vomited 1 or 2 times 2 hr. before entry; pallor (but did not appear severely ill, no manifestation of dehydration); tonsillitis and pharyngitis, subacute	39.2	11,800

TABLE I—CONT'D

CASE	AGE	SALICYLATE RECEIVED	SYMPTOMS AND SIGNS	TEMPERATURE ON ADMISSION (°C.)	TOTAL WBC
8	20 mo.	8 tsp. daily; unknown medication for 2½ days	Fever, 4 days; cold (unknown medication for 2½ days); twitching 12 hr. before entry; deep pauseless respiration, moderate; acute otitis media, right ear	40.0	7,200
9	5 mo.	30-60 grains in 3 days (aspirin)	Cold, 1 week; fever, 3 days (aspirin started 3 days before entry, ¼-½ tablet every 3 hr.); restlessness and irritability, 8 hr.; hyperpnea, 8 hr.; listless and drowsy on entry; rhinopharyngitis and tonsillitis; petechiae over chest; bloody emesis, 20 c.c.	37.7	9,300
10	2 yr.	126 grains in 3 days (aspirin)	Upper respiratory infection, 3 days (A.P.C. tablets every 2 hr. for 3 days); hyperpnea 1 day before entry and continued 24 hr. after entry and treatment	38.0	14,000
11	21 mo.	Accidental consumption of unknown amount of liniment	Hyperpnea; listlessness; moderate dehydration	37.5	17,100
12	3 yr.	Same as above (siblings)	Hyperpnea, slight; disorientation, slight; ataxia, slight	37.0	10,000
13	3½ yr.	24 grains of aspirin in 2 days	Headache, fever, vomiting, 6 days; sore throat, 3 days; listlessness, 3 days; hyperpnea, slight (noted on admission); tonsillitis	37.8	7,000

*History of Present Illness.*—The patients were admitted with a history of "cold" and, in some instances, cough for from four to seven days. All of them had received salicylates (definitely known to be aspirin in eleven cases) in large dosages for at least one to four days prior to admission. Liniment containing salicylate was accidentally ingested by two Negro siblings. Abnormal breathing was noted by the parents and described as deep and pauseless. This abnormality in respiration was seen from eight to sixty hours before hospitalization, and either accompanying or, more often, following the onset of this change in respiration, there was listlessness which rapidly became more pronounced. Vomiting occurred in five of the patients in addition to marked anorexia. This decrease in caloric and liquid intake continued for as long as three days prior to entry.

*Clinical Findings.*—The appearance of the patients was that of ill or severely toxic infants or young children. Although no temperatures were taken by parents, rectal temperatures of nine of these patients varied between 38 and 40° C. on admission. All of the patients were either very pale or cyanotic; most were slightly or moderately dehydrated and apathetic; the younger and smaller ones were more often semicomatose or stuporous. All manifested abnormal respiration. Respirations were exaggerated in depth and followed one another with little or no intervening pause.

The youngest and smallest patient of this series (Case 1, Table I) demonstrated hemorrhagic tendencies manifested by epistaxis, tarry stools, and xanthochromia of the spinal fluid. The aspirin was administered approximately three and one-half days before entry, and the bleeding tendencies were noted within the first day of hospitalization. The prothrombin time was prolonged.

One of the patients had generalized convulsions during the first three days of hospitalization; two others developed mild twitchings three and twelve hours before admission respectively.

Infections of the respiratory tract were noted in eleven of the patients and verified as relatively mild inflammations which are not accompanied by hyperpyrexia and febrile convulsions.

TABLE II. PROTHROMBIN LEVELS IN PATIENTS WITH SALICYLATE INTOXICATION

CASE	AGE	SALICYLATE LEVEL OF PLASMA (MG.%)	PROTHROMBIN LEVEL		HEMORRHAGIC MANIFESTATIONS
			PATIENT	CONTROL	
1	3 wk.	68.5	4'51"	1'5"	Petechiae Epistaxis Melena Xanthochromia of and crenated red cells in the spinal fluid
2	6 mo.	44.4	45"	55"	
3	26 mo.	40.0	2' 0"	1'15"	
4	8 mo.	65.2	1'45"	45"	
5	4½ mo.	42.3	40"	30"	Hemorrhage into both ventricles (post-mortem ventricular taps)
6	3½ mo.	41.6	70"	30"	
7	2½ yr.	18.2	35"	35"	
8	20 mo.	7.3	28"	31"	
9	5 mo.	20.8 12 hr. later 13.3 2 days later 3 days later	1'55" 2' 0" 50" 27"	40" 30" 30" 30"	Petechiae over chest and bloody emesis
11	21 mo.	15.9	38"	45"	
13	3½ yr.	7.3 3 day 0.35	10' 0" 60"	1'40" 50"	

*Laboratory Findings.*—The most outstanding laboratory findings concerned the changes in the acid-base equilibrium of the blood. The carbon-dioxide content of the serum of these patients before treatment was uniformly depressed with a consistent lowering of pH. The younger patients showed more profound changes in this shift to acidosis than the older ones. The next most consistent laboratory feature (Table II) was a prolongation of prothrombin time in six of the eleven patients. Clinical evidence of hemorrhage was noted in only two patients. Electroencephalograms were done on three patients; one showed abnormal tracings on the twelfth day of hospitalization. Three months later they were still abnormal; however, normal tracings were obtained nine months after

hospitalization.\* Serum chlorides were usually normal or elevated; only two were slightly below normal. The majority of glucose determinations yielded normal values. The initial nonprotein nitrogen values were slightly elevated. In one instance (Case 5) there was evidence of renal failure with 118 mg. per cent nonprotein nitrogen, 8 mg. per cent calcium, and 7.5 mg. per cent inorganic phosphorus. This patient died, and no autopsy was obtained. Urinary findings included albuminuria, positive Rothera test and persistence of positive ferric chloride test on boiling, as well as many granular casts on microscopic examination. Cases 11, 12, and 13 (Table III) showed low urine pH values before treatment; succeeding values on the second and third days of hospitalization showed a rise in urinary pH. On the third day of hospitalization there was still a positive Rothera test as well as a persistent though decreasingly positive ferric chloride test on boiling of the sample.

TABLE III. URINARY FINDINGS IN PATIENTS WITH SALICYLATE INTOXICATION

CASE	DAY OF HOSPITALIZATION	SALICYLATE LEVEL IN PLASMA (MG.%)	FeCl <sub>3</sub>	URINE		
				ROTHERA	pH	Chlorides Gm. NaCl/ L. Urine
10	1	38.8	+++	+++	--	--
	2	21.4	+++	+++	--	--
	4	3.2	+++	++	--	--
	5	----				
11	1	15.9	---	+++	5.0	1.4
	2	----	+	+++	6.0	1.1
	3	0.6	trace	++	7.0	--
12	1	1.7	±	+++	4.5	3.4
	16 hr. after admission	1.3	±	+++	5.0	3.4
	2	0.2	-	+	7.0	--
13	1	7.3	+++	+++	5.19	--
	2	1.35	±	+++	5.0	--
	3	0.35	trace	--	7.0	--

The spinal fluid was examined in nine of the cases and showed a positive Rothera test as well as ferric chloride, even with boiling of the sample. In only one case (Case 1) were crenated red blood cells as well as xanthochromia noted.

Total ketones as acetone and base-binding ketones of the blood were determined in Case 10. The base-binding ketones amounted to 11 milliequivalents per liter. The significance of this is apparent when one observes that the bicarbonate value is depressed from normal value of 20 to 25 milliequivalents per liter to approximately 12 milliequivalents per liter.

*Salicylate Determinations.*—Plasma salicylate determinations showed at the time of entry, levels of 40 mg. per cent and higher in the younger patients who demonstrated the most severe type of intoxication. Lower concentrations were found more frequently in the patients older than 20 months. In almost all of these instances the initial pH of the serum was low normal or slightly below normal with corresponding carbon-dioxide content of the serum between 25 and 35 volumes per cent. The highest concentration of salicylate in

\*This patient never has had epileptic manifestations, either before salicylism or up to June, 1946.

the plasma, 68.5 mg. per cent, was found in the 3-week-old infant who had received a total of 1.5 Gm. of aspirin in two days. Table IV shows the amount of salicylate administered to each patient insofar as it was possible to gain this information. For comparison, there are tabulated the dosages recommended by Marriott and Jeans<sup>7</sup> for infants. In most of these patients the doses administered were greater than that within the range of safety calculated by Marriott and Jeans. Some of these patients received dosages of salicyl compounds as great as those dosages recommended for therapy in acute rheumatic fever in older children<sup>8</sup> and for young adults.<sup>9</sup>

TABLE IV. COMPARISON OF ASPIRIN DOSAGES RECEIVED WITH THOSE RECOMMENDED AS SAFE

CASE	MAXIMUM RECOMMENDED* DOSE (GRAINS/DAY)	MAXIMUM DOSE RECEIVED (GRAINS/DAY)	DURATION OF MEDICATION (DAYS)	SALICYLATE LEVEL OF PLASMA (MG.%)
1	½	11¼	2	68.5
2	3	27	1	44.4
3	13	7½	2	40.0
4	4	8 pills daily (?)	4	65.2
5	2	17	3½	42.3
6	2	10-15 (mother vague)	1	41.6
7	15	22½	2	18.2
8	11	8 tsp. unknown medication	2½	7.3
9	2½	10-20	3	20.8
10	12	42	3	38.8
13	21	12	2	7.3

\*On basis of amounts recommended by Marriott and Jeans—1 grain per year of age every four hours.

*Therapy.*—All of the patients except one received M/6 sodium r-lactate in Ringer's solution by the intravenous and subcutaneous routes immediately on admission to the hospital in amounts indicated in Table V as cubic centimeters of M/1 sodium r-lactate per kilogram of body weight. A five per cent glucose solution was given hypodermically and in most instances at several intervals by intravenous and subcutaneous routes until oral feeding could be resumed. Parenteral vitamin K and vitamin C were given to all patients. In addition to vitamin K, small whole blood transfusions were used to combat hemorrhagic tendencies.

The patients in severe acidosis were also in a state of circulatory collapse, and though their respirations were exaggerated, their skin was ashen gray. Oxygen was given to these patients, and they were bundled in warm blankets; however, the restoration of fluids and electrolytes did more to overcome the state of circulatory collapse.

*Course.*—The response to treatment varied in each of these patients, and all except two of them showed clinical improvement to some degree in one to two hours following treatment. One of these patients (Case 5) died; the other (Case 13) showed no improvement with glucose and M/40 lactate Ringer's solution for twenty-two hours; response was good after M/6 sodium lactate solution was given (Table V). Those who were treated for severe acidosis, who were in a state of circulatory collapse, and who had high levels of salicylate, were slow to overcome their lethargy even though they were no longer comatose. This is in contrast with the usual rapidity with which the

TABLE V. BLOOD CHEMISTRY STUDIES BEFORE AND AFTER TREATMENT

CASE	TIME	M/1 Na-r- Lactate c.c./Kg.*	MG.% SALICYLATE		SERUM pH	CO <sub>2</sub> CONTENT (SERUM VOL.%)	SERUM CHLORIDE (Mg.% NaCl)
			PLASMA	SPINAL FLUID			
1	1 P.M.	10	68.5	17.5	7.13	15.8	631
	4½ hr.	5	38.2		7.41	47.0	
	21 hr.		35.6	9.4	7.41	50.4	
	II day		20.9		7.47	58.5	
	III day		8.0		7.55	64.5	
	IV day		trace		7.58	74.8	
2	12 P.M.	15	44.4	15.7	7.20	16.7	680
	9 hr.		33.6		7.51	51.6	
	II day		1.5		7.49	60.5	
	V day		trace				
3	11 A.M.	9	40.0	11.8	7.33	25.8	
	5 hr.		35.4		7.50	43.5	
	22 hr.		23.1		7.51	50.8	
4	1 P.M.	15	65.2	26.0	7.20	20.4	
	7½ hr.				7.46	36.7	
	20 hr.		42.6		7.47	63.0	
5	9 A.M.	5	42.3	14.6	7.27	16.0	703
	1 hr.				7.30	29.0	
	2½ hr.				7.43	35.0	
	4½ hr.				7.52	36.0	
	7 hr.				7.48	47.0	
6	6 P.M.	11	41.6	8.0	7.16	14.0	679
	16 hr.				7.32	51.0	
	23 hr.		29.5				
	II day		9.7				
	III day		3.2				
	IV day		0.8				
7	9 P.M.	9.2	18.2	3.2	7.30	26.0	580
	13 hr.		13.2		7.50	59.8	
	II day		trace				
8	on admis- sion	5	7.3	1.04	7.32	31.0	
9	12:10 A.M.	5	20.8	6.25	7.32	38.0	560
	12 hr.		13.3		7.50	57.8	512
	24 hr.					66.0	568
10	3:30 P.M.	8	38.8	17.0		26.5	590
	4½ hr.					49.4	
	17½ hr.		30.6		7.38	45.6	
	23½ hr.				7.43		
	41½ hr.		21.4				
	58 hr.						
	65 hr.		11.8		7.46	60.6	
	89½ hr.		3.2			73.0	
	113½ hr.					76.3	
11	5 P.M.	10	15.9		7.31	20.0	594
	16 hr.		2.3		7.38		580
	23 hr.					55.5	
	48 hr.		0.6		7.43	60.0	572
12	5 P.M.	5	1.7		7.31	34.0	570
	16 hr.		1.3		7.44	51.5	571
	40 hr.		0.2		7.45	62.0	604
13	2 P.M.		7.3		7.32	37.0	540
	21½ hr.	10	1.33		7.35	36.0	552
	45½ hr.		0.35		7.44	56.0	570

\*Sodium-r-lactate diluted to M/6 in Ringer's solution. Patients also received glucose parenterally.



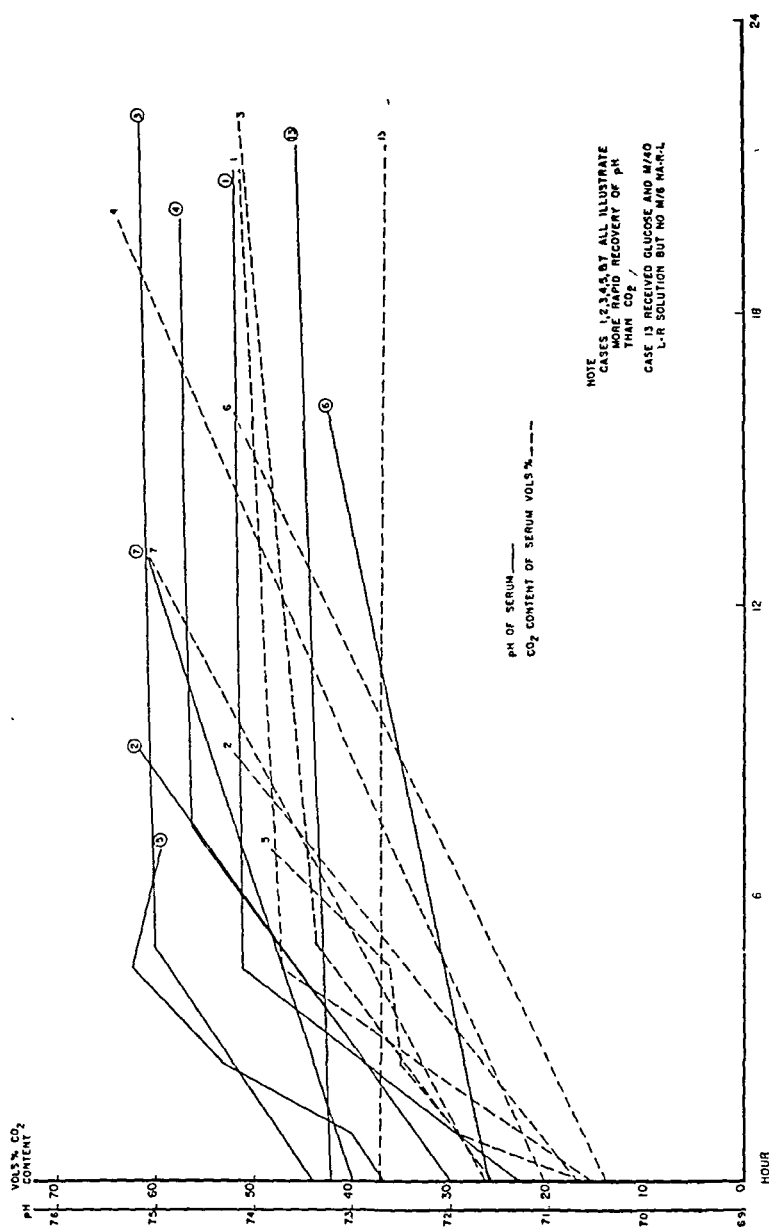


Fig. 1.—Illustration pH and carbon dioxide before and after treatment of metabolic acidosis from salicylate intoxication (Cases 1 to 7, and Case 13).  
(Case 13. This patient was given M/6 sodium r-lactate immediately following the last determination of serum pH and carbon dioxide represented in this figure.)

diabetic who has just recovered from acidosis quickly overcomes his lethargy. In Fig. 1, showing the individual recoveries of the patients, and in Table V it is shown that the pH of the serum returned to the range of normal before the carbon-dioxide content (principally bicarbonate) of the serum was restored to the range of normal. A similar pattern of restoration of acid-base balance has been observed in diabetics<sup>10</sup> whose recovery from acidosis has been studied by the method of Shock and Hastings.<sup>11</sup> The cause here would seem to be continued hyperpnea on the basis of salicylate in spite of relief of acidosis.

Rapid recovery (Table V and Fig. 1) of acid-base equilibrium was uniform except in the two instances (Cases 5 and 13) mentioned. Cases 1, 3, and 10, within five hours after treatment, showed restoration of the pH and carbon-dioxide content of the serum to normal. In contrast to the rapid recovery of acid-base equilibrium, the salicylate disappeared slowly from the blood, and appreciable amounts were found on the second and third days of hospitalization as can be seen in Table V.

*Mortality.*—All but one of these patients showed an ultimately good clinical response to therapy given. This was the patient (Case 5) who had elevated non-protein nitrogen of 118 mg. per cent. He was 4½ months old and expired eleven hours after admission. At the time the last laboratory determinations were available, the patient's acid-base equilibrium was found to be within normal range; serum pH was 7.48, and the carbon-dioxide content had risen to 47 volumes per cent. Although this restoration of acid-base equilibrium proceeded gradually, as can be seen from Table V, there was no coincident improvement in the clinical condition of the patient. The initial sample of spinal fluid gave no signs of hemorrhage; however, post-mortem intraventricular taps showed bloody fluid despite administration of vitamin K. No necropsy data are available.

#### EXPERIMENTAL STUDIES

Several older children were given salicylate experimentally as aspirin or sodium salicylate for three to six consecutive days. These children were from 5 to 12 years of age, and as a group demonstrated different effects of salicylate on respiration, pH, and carbon-dioxide content of the serum. The results are given in Table V. Case E1 exhibited severe hyperventilation on the third day; however, the serum pH was at the upper limits of normal and the carbon-dioxide content slightly depressed. Case E5 had only slight hyperpnea, but developed severe anorexia and vomiting with marked lowering of pH and carbon-dioxide content as can be seen in Table VI. Case E7 showed no effect at all, even on the sixth day when the concentration of salicylate was 35.8 mg. per cent in her plasma. She was the oldest of these four patients. It should be emphasized that all of these patients had good caloric and liquid intake prior to and during administration of salicylate, and only as mentioned in Case E5 was there severe anorexia and vomiting.

The absorption of aspirin and sodium salicylate following single and multiple oral doses was studied in a group of children. From the absorption curves of both sodium salicylate and aspirin on patients with varying single doses (see Figs. 2 and 3) it appeared that there would be an accumulation of

the salicyl compound when given at the usually advised interval of every four hours. These compounds when so given for several days did show an increase in the level from day to day (Fig. 4). The actual accumulation was tested on a single subject and compared with the hypothetical effect. This was done by giving a single dose (.043 Gm. per kilogram) of sodium salicylate by mouth and observing the gradual rise and fall of the plasma salicylate level. The rate of absorption was slow because enteric coated tablets were used. Following this procedure a second test was performed by giving the same dose of sodium salicylate every four hours. At the end of twenty-four hours the experiment was terminated because the subject experienced tinnitus and nausea and began to vomit. The actual values obtained during the second test are plotted in Fig. 5 on the broken line curve and do not deviate much from the hypothetical curve showing accumulation by superimposition of the single dose absorption curve at four-hour intervals.

TABLE VI. VARIOUS REACTIONS TO SALICYLATE AS SEEN IN OLDER CHILDREN GIVEN THE DRUG EXPERIMENTALLY

CASE	AGE	DOSE (GM./KG./ 24 HR.)	DURA- TION (DAYS)	MAXIMUM SALICYLATE LEVEL OF PLASMA (MG.%)	pH	CO <sub>2</sub> (VOL.%)	HYPER- VENTILA- TION	ACID- BASE REACTION
E1	10	.17 Na salicylate	3	48.5	7.45	40.4	severe	early re- spiratory alkalosis
E5	6	.19 Na salicylate	6	54.2	7.25	23.8	slight	metabolic acidosis
E6	5	.30 Na salicylate	4	55.4	7.31	24.4	moderate	metabolic acidosis
E7	12	.12 aspirin	6	35.8	7.41	45.6	none	normal

#### DISCUSSION

In order that an infant or young child not be allowed to become seriously intoxicated with salicylates, it would be well for physicians and especially pediatricians to educate and warn parents of these potential properties of aspirin and other salicylate compounds. This is done and wisely so in the case of the sulfonamide compounds. Why is it not done with salicylate compounds?

Certainly the use of salicylate compounds for purposes other than symptomatic relief is not justified. Infection should be combated by specific measures. Almost all drugs have untoward effects, and these are proportionately intensified with larger doses. In therapeutics, these harmful effects must not outweigh the beneficial effects if drugs are to be used advantageously. Even with supervision in administration of salicylates in older and larger children who are capable of making known their complaints, the medication can produce serious and sometimes fatal intoxication.<sup>12</sup>

Stevens and Kaplan<sup>12</sup> found that children of ages 9 to 11 did not tolerate the massive doses of salicylate which achieved blood plasma levels considered by Coburn<sup>8</sup> to be therapeutically beneficial yet unharmed in adults. They also observed that it was not easy to maintain the concentration of salicylate and that it was necessary to manipulate the dosage from day to day and de-

termine the actual concentration in the plasma. Furthermore, they stated that the drug accumulated, and it was because of this that they found it necessary to alter the dosage. The efficacy of this massive dosage is questioned by Wégria and Smull.<sup>13</sup> Fashena and Walker<sup>14</sup> also demonstrated that the dosages could be decreased by 30 to 35 per cent of the initial twenty-four hour dose without significantly altering the concentration of salicylate in the blood plasma. Guest and associates<sup>15</sup> found that the effect of salicylate appeared to be proportional to the dose administered, and also noted that this effect increased with the duration of medication. We have shown that there may be an accumulation of salicylates in the blood from day to day.

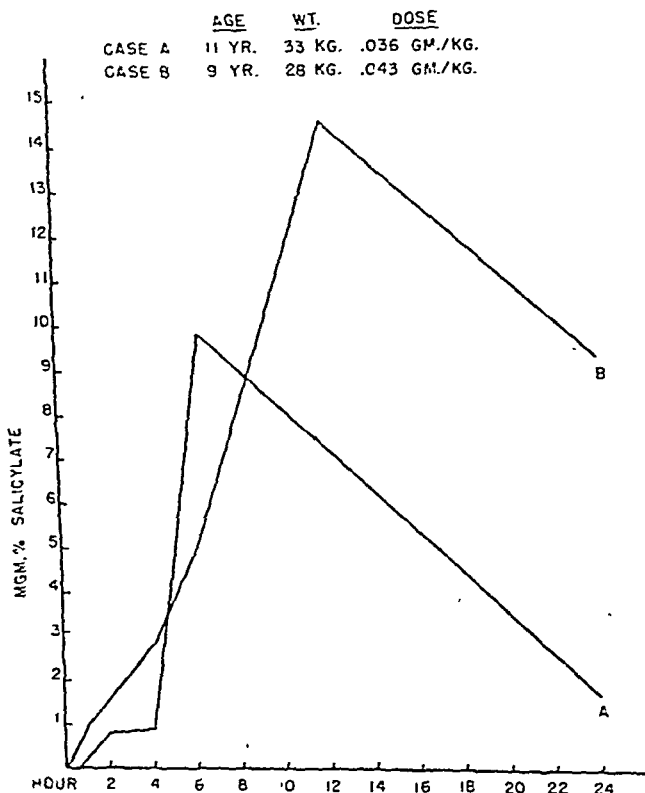


Fig. 2.—Rate of absorption of oral sodium salicylate (single dose). Salicylate values apply to plasma concentrations.

Because of the serious and progressive nature of salicylate intoxication, the evident necessity for an early diagnosis, especially in infants, cannot be overemphasized. By far the most common symptoms of poisoning in this very young group of patients were hyperpnea, fever, listlessness, and even coma, pallor, and cyanosis. With the listlessness came disinterest in feeding procedures. Less prominent were dehydration, which was slight to moderate, vomiting, and convulsions. Two patients presented clinical evidence of hemorrhagic phenomena, and in another patient hemorrhage into the ventricles was found on post-mortem intraventricular puncture.

In the absence of renal failure, diarrhea, diabetes, and other severe infections, the combination of hyperpnea, listlessness, and fever should suggest salicylate intoxication as a likely diagnosis. A more direct approach to the problem of an early diagnosis can be achieved by obtaining a careful history of medications given to the patient. Since fever is such a prominent finding, as noted by Dodd and associates<sup>16</sup> and Barnett and associates,<sup>1</sup> the error of giving salicylates as supportive treatment to alleviate hyperpyrexia can best be avoided by ascertaining the diagnosis first. It is entirely possible that many of our cases of intoxication resulted from prolonged use of aspirin for fever which in reality became a toxic

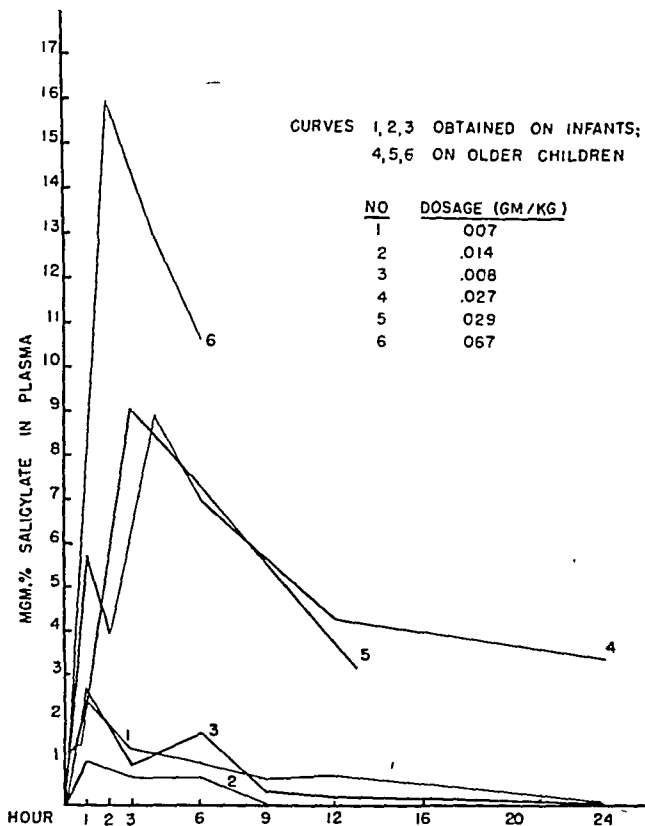


Fig. 3.—Rate of absorption of aspirin (single oral dose).

manifestation of aspirin. This clinical picture together with the laboratory findings of distorted acid-base balance and positive urine ferric chloride test on boiling confirms the diagnosis. A determination of plasma salicylate will complete the picture. Other procedures may reveal other toxic effects from salicylate, such as prolonged prothrombin time,<sup>17-19</sup> hypocoagulability of the blood,<sup>20</sup> epistaxis,<sup>21</sup> hemorrhages into the stomach<sup>22, 23</sup> and brain,<sup>24</sup> granulocytopenia,<sup>25</sup> toxic hepatitis,<sup>26</sup> low vitamin C content as found in animal tissues by Ritz and associates,<sup>27</sup> or increased vitamin C output into the urine,<sup>28</sup> and even lowered renal clearance<sup>29</sup> and evidence of renal damage which may be temporary.<sup>30</sup>

The general condition of most of these young patients gives indication of the need for prompt treatment. Therapy includes treatment of acidosis by administration of M/6 sodium r-lactate in Ringer's solution and glucose parenterally; relief of dehydration and ketosis is also achieved by this procedure. Case 13 clearly illustrated the response of a patient in acidosis when treated with glucose and M/40 lactate Ringer's solution instead of M/6 sodium r-lactate in Ringer's. The carbon-dioxide content of the serum and pH of the urine remained abnormally low for twenty-two hours, and they did not respond until a full dose of M/6 r-lactate was given. (Tables III and V.) Dodd and associates<sup>16</sup> considered alkali useful for treatment late in the course of intoxication when acidosis developed. Rapoport and associates,<sup>31</sup> in testing the effect of sodium bicarbonate on salicylate intoxication in dogs, observed that the

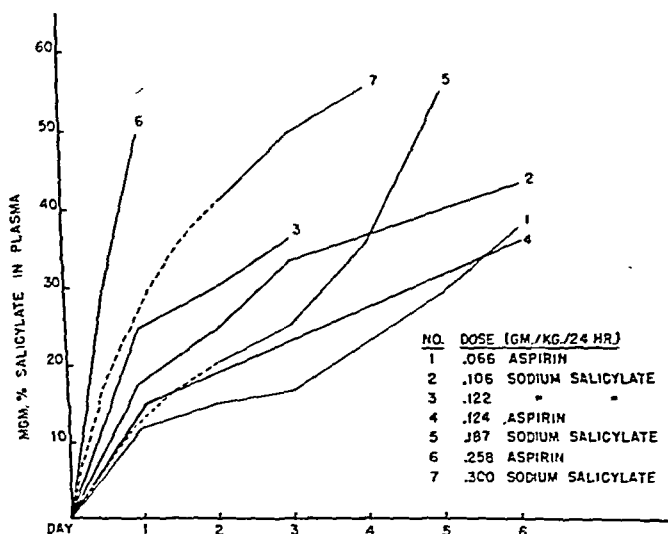


Fig. 4.—Plasma concentration of salicylate with oral aspirin and oral sodium salicylate (divided doses at four-hour intervals).

duration of the intoxication was shortened in spite of an already existing tendency for respiratory alkalosis. One of their animals did develop fatal tetany. Vitamin K and small, whole blood transfusions are indicated on the basis of the ever increasing evidence of hemorrhagic phenomena reported in the literature,<sup>14, 32</sup> and our own findings. Without studies prior to the onset of salicylate intoxication, it is not possible to evaluate the need for vitamin C; however, the work of Ritz and associates<sup>27</sup> and Daniels and Emerson<sup>28</sup> and the usual history of the patient serve to provide rationale for parenteral and later enteral vitamin C. Undue exposure of these patients should be avoided in spite of hyperpyrexia. The use of cool oxygen is not contraindicated and appears to be stimulating. Whenever there has been a history of recent ingestion of a large amount of aspirin or other salicylate compound, gastric lavage is a very important procedure and should not be omitted.

Serum pH and carbon-dioxide determinations can be repeated at four- to six-hour intervals following treatment if the patient seems to be doing well

clinically. These should be done more frequently if indicated, and additional lactate may be necessary if the patient is severely acidotic, although the majority of our patients did not need additional M/6 sodium lactate solution. Early in the course of treatment, color, responsiveness, and activity are better criteria of clinical status than respirations. The reason for this is that with the administration of fluids the patient seems to obtain a "second wind" and can improve respiratory efforts in attempting to blow off excess carbonic acid. Therefore, with the improvement in the general condition of the patient, he responds to the physiologic demand for increased respiration. Following the

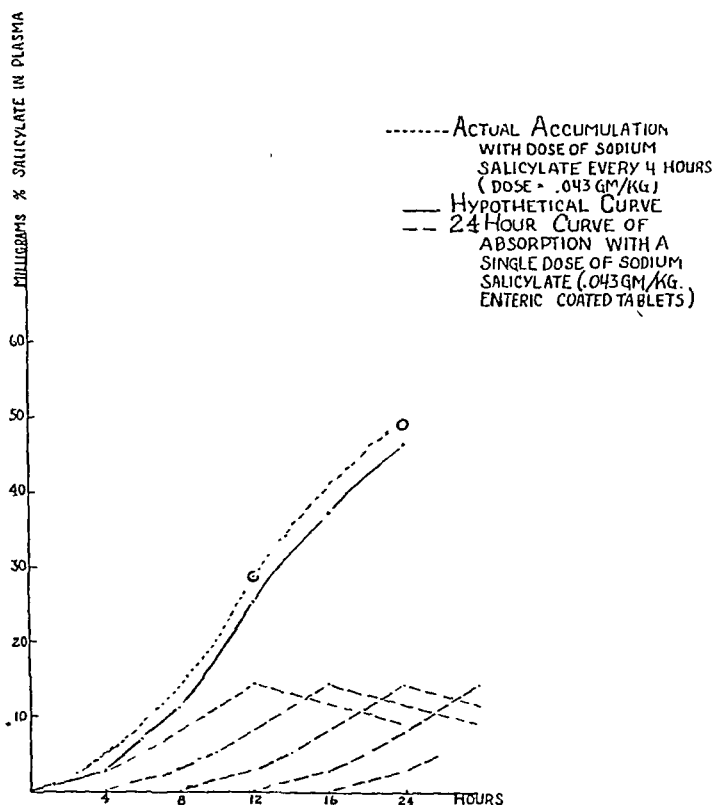


Fig. 5.—Cumulative effect of salicylate.

establishment of the proper ratio of sodium bicarbonate and carbonic acid concentrations and relief of ketosis, if there be sufficient concentration of salicylate, hyperventilation will continue because of the apparent, direct, stimulating effect of the salicylate.

The toxic manifestations due to salicylates are manifold, and, moreover, the incidence of a given symptom appears to vary in the different age groups. For example, we have named the most common symptoms associated with severe and acute intoxication in infants which, of course, do not include such complaints as vertigo, tinnitus, headache, and deafness. These are correlated with the ability of self-expression. Other reactions described in the literature

and not yet mentioned include urticaria, anaphylactic reaction, and gastrointestinal irritation which may be associated with gastric ulceration and toxic encephalopathy. Coburn states that there was no evidence of prolonged prothrombin time in his patients who were adults.<sup>9</sup> There is evidence from the literature<sup>14</sup> as well as from our own data (Table II) that this occurs in children and infants.

The literature has become confused, particularly with reports which would seem to be conflicting because one or another form of acid-base imbalance is emphasized. A part of this confusion may arise because the determination of carbon-dioxide content of the serum is not supplemented by a pH determination of the serum and urine; part of it may also arise because an attempt is made to compare results on anorexic younger children and infants with experimental results obtained on older children, adults, and even animals, whose usual caloric and liquid intakes have not been affected prior to or during the period of study. These results cannot be applied interchangeably. Ketosis, for example, occurs with greater rapidity in children than in adults. Emphasis should rather stress the different kind and degree of salicylate intoxication that is developed in individuals, as we have shown in our experimental group (Table VI).

The evidence of a respiratory type of alkalosis similar to that developing in the first case of the experimental group (E1, Table VI) has been seen also in the older individuals on which it is presumed that Odin<sup>34</sup> bases his conclusions, since he does not designate the age group that received such large doses of salicylate. Coburn,<sup>9</sup> however, found no such effect. A shift of acid-base balance to respiratory alkalosis was observed by Ryder<sup>35</sup> in one case of a 16-year-old Negro patient, and by Guest and associates<sup>15</sup> in children 3 years of age and over. In dogs, Dodd and associates<sup>16</sup> found only a slightly elevated pH in a phase of panting. Dodd, however, did not find too great a similarity in the pattern of intoxication in dogs and infants. In experiments on monkeys and dogs, Rapoport and associates<sup>31</sup> found primary hyperventilation with lowering of carbon-dioxide tension in blood with or without decrease in bicarbonate. They also observed that pentobarbital sodium could suppress hyperventilation and restore pH and carbon dioxide to normal values. Morphine exerted a convulsant action without noticeable decrease of hyperpnea. The general condition of the dogs in the experiments of Dodd and associates<sup>16</sup> was remarkably good; the dogs ate eagerly and drank unusually large amounts of water throughout the entire experiment. This reaction is so strikingly different when contrasted with the pattern of reaction exhibited in young children and infants and is of such significance, that it must be emphasized. By the same token, reactions and tolerance exhibited by the adults preclude a fair transference or application of data obtained on such a group with that obtained in a group of young children or infants. Decreased intake of food, liquids as well as nutritious substances, is a key factor in the production of metabolic acidosis in infants. Sable<sup>30</sup> proposed that the ketonuria and ketonemia may be due to starvation from anorexia and vomiting or the toxic effect on cellular metabolism. Lutwak-Mann<sup>38</sup> found that respiration of rat liver and kidney



slices is inhibited by M/10 concentration of salicylates, and that liver glycogen disappeared almost completely four to six hours after salicylate injection. Similar work has not been done on human tissues.

To conclude the discussion of this difference in toxic effect of salicylate which exhibits one pattern of acid-base imbalance in a group of infants and a more variable pattern in the experimental group of older children, it may be said that there is a cycle which can be interrupted or aggravated at any phase. To understand the pattern of a given patient, many determinations can be done, but the most significant data are obtained from values of urine pH, blood pH and carbon dioxide. The cycle, from all available information, is one of hyperventilation caused by salicylate, uncompensated respiratory alkalosis, then compensation rapidly brought about by the kidney with excretion of excess bicarbonate. Ketosis, which may be present even before administration of salicylate, but is certainly aggravated by it, produces a shift toward metabolic acidosis. Since hyperventilation caused by salicylate (either by central or reflex stimulation) is already in operation, it soon begins to fail because of muscular fatigue and lethargy which are early and prominent factors in the infant. The onset of metabolic bankruptcy on the basis of starvation and increased metabolism takes its toll more quickly in the infant. With the depletion of sodium bicarbonate enhanced by ketosis, it becomes even more imperative for hyperventilation to continue, so that there will not be a relative excess of carbonic acid. At this point, when hyperventilation has become a physiologic necessity and not merely a manifestation of salicylism, the respiratory center may have undergone poisoning, or the patient may lag because of the inability to keep apace with all that has transpired. If either of these factors operates (and it can be readily understood that the infantile tissues cannot cope as long with such odds as the adult), then metabolic acidosis ensues. On the average, respiratory efforts seem only 50 per cent efficient. In the early phase of the cycle, urinary pH is alkaline, coinciding with excretion of sodium bicarbonate; however, later, the pH reverts to acid values coinciding with the phase of metabolic acidosis.

#### CONCLUSIONS

1. Thirteen cases of salicylate intoxication in infants and very young children are discussed.

2. The most severe type of reaction occurring in this group is a disturbance of the acid-base equilibrium. Other types of reactions were encountered less constantly.

3. At the time of hospitalization, all patients showed a metabolic acidosis with a lowered pH and carbon-dioxide content of the serum.

4. Salicylates, given experimentally to older children whose usual caloric and liquid intake were maintained, produced less regular, if any, signs and symptoms of toxicity.

5. Salicyl compounds, when given in dosages from 0.066 Gm. per kilogram per twenty-four hours in six divided doses (approximately  $\frac{1}{2}$  grain per pound),

tend to accumulate in significant amounts in the body, as shown by determinations of plasma levels.

6. In view of the dangers and possibility of fatality in infants, it is suggested that aspirin be given not at all or very cautiously, with full awareness of all its properties for intoxication. These same possibilities for intoxication in one form or another obtain in older individuals, but to a lesser degree.

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## TUBERCULOUS DACTYLITIS IN CHILDHOOD: A PROGNOSIS

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THE spontaneous healing of remarkably destructive tuberculous lesions of the small bones of the hands and feet (metacarpals, metatarsals, and phalanges) observed over the past decades in the Harriet Lane Home has led to the present study of cases recorded in the diagnostic index of the clinic. Twenty-one cases were selected for analysis because of adequate clinical and laboratory examination and follow-up.

Each patient reacted positively to intradermal, tuberculin skin testing and had a negative blood Wassermann test. All but three showed roentgen-ray evidence characteristic of pulmonary or mediastinal tuberculosis. All patients were below the age of 14 years when first examined in the Harriet Lane Home. Nine of the twenty-one patients gave a history of exposure to sputum-positive tuberculosis.

*Incidence.*—In the special tuberculosis clinic where 610 children infected with tuberculosis under 2 years of age have been registered since 1928, tuberculous dactylitis has been recognized in only four patients, giving an incidence of 0.6 per cent. In addition, since only forty-three cases in all have been recorded during the past three decades at the Harriet Lane Home where the incidence of tuberculosis is quite high, it is apparent that tuberculous dactylitis is a relatively rare complication. This is in rather marked contrast to the figures of Herzfeld and Tod<sup>1</sup> (6 per cent) and of Benci and Mezzari<sup>2</sup> (4.21 per cent).

From a clinical viewpoint the patients fall into two groups: Group I consists of eleven individuals who had tuberculous dactylitis as a minor manifestation of a severe generalized infection;† Group II includes ten patients who had a relatively mild tuberculous infection and whose dactylitis, the presenting symptom in eight instances, was one of the minor complications.‡

*Color, Age, and Sex.*—There is no significant difference between the two groups with respect to color, age, and sex. It is of interest, however, that sixteen (76 per cent) of the total number of patients were negro. It is significant that fourteen (67 per cent) were under 2 years of age at the time when this complication was observed. This conforms with Dr. Brailey's<sup>3</sup> findings demonstrating that tuberculosis is a more severe disease in infancy than in later childhood.

*Length of Follow-up.*—The average length of life after recognition of the disease of the patients in Group I (with the exceptions noted above) was two and one-half years, with a minimum of seven days and a maximum of five years.

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†All but three of these patients subsequently died of tuberculosis. Two of these may be presumed to have died because of the presence of very extensive lesions when last seen. The third patient is still alive after twelve years, but has numerous, active, tuberculous lesions.

‡The tuberculous lesions of these patients healed completely and, with one exception, left no residual disability or deformity, as the accompanying x-rays show. With the exception of one child who died of pyogenic meningitis, all of these individuals are living and well, and at present show no evidence of active tuberculosis.

The follow-up of the children in Group II averaged eleven years, with a minimum period of one and one-half years and a maximum of twenty-eight years.

*Primary Tuberculous Lesions.*—As a whole, children in Group I appeared more ill and had more extensive tuberculous lesions than those in Group II. As Table I shows, in Group I eight of the eleven patients had severe pulmonary lesions; the remaining three showed marked enlargement of the mediastinal nodes. However, in Group II only two of the ten patients had parenchymal lesions, five had enlarged mediastinal nodes, while three had only slight, non-specific infiltration at the lung roots.

TABLE I. FINDINGS ON ROENTGEN-RAY EXAMINATION OF CHEST OF TWENTY-ONE CHILDREN WITH TUBERCULOUS DACTYLITIS

GROUP	TOTAL NO.	PARENCHYMAL PULMONARY TUBERCULOSIS	MEDIASTINAL TUBERCULOSIS	NONSPECIFIC ROOT INFILTRATION
Group I	11	8	3	0
Group II	10	2	5	3

*Clinical Picture.*—The local clinical picture was essentially the same in both groups of patients. The infected phalanx presented a fusiform, indurated swelling, usually painless. Fluctuation was present if the tuberculous lesion had broken through the periosteum of the bone with resultant abscess formation. The overlying skin was usually taut, shiny, and red. In only one instance was there a preceding history of trauma. Fistulas formed in eight lesions. Where the metacarpal or metatarsal bones were involved, the swelling appeared mainly on the dorsal surface, the area where the three fistulas recorded also appeared. Quite significantly, the "painless swelling" of the fingers was the presenting complaint in eight of the ten patients in Group II and of three in Group I, while other symptoms of a tuberculous infection were the chief complaint in the remaining eight. The average duration of the dactylitis before examination was two months in Group I and four months in Group II. However, the dactylitis was either the presenting complaint or an early sign in nineteen of the twenty-one children studied.

*Other Types of Tuberculous Complications.*—All eleven patients of Group I had other complications of the primary tuberculous infection, the most common, apart from serious involvement of the lung parenchyma in eight instances, being infections of other bones (radius and ulna three, tibia three, mandible three, spine two, orbit one, humerus one, and sternum one), cervical adenitis six, skin tuberculids two, and peritonitis one. The predominant tuberculous infection was bone and joint tuberculosis (eight patients) and miliary tuberculosis (three patients). However, five, or one-half of the children in Group II, had no evident complications other than dactylitis. Of the remaining five, involvement of other bones (radius and ulna two, spine one, and tibia one), bilateral phlyctenular keratitis one, cervical adenitis one, and peritonitis one, constitute the known complications.

*X-ray Findings.*—(See Figs. 1 to 14.) From the accompanying photographs of x-ray plates and films, one may see that the tuberculous lesions of the small bones assume many varied forms, from minimal medullary changes and periosteal



Fig. 1.—L. B., aged 2 years, with severe pulmonary tuberculosis and multiple metastatic tuberculous bone lesions. Destructive lesions are seen in ten of the small bones of the hands; soft tissue swelling is seen in the neighborhood of the more severely involved bones.



Fig. 2.—L. B., aged 5½ years, showing good partial healing of the lesions in the right hand but progression of the lesion in proximal phalanx of the index finger, left hand.

reduplication, said to distinguish tuberculosis of the phalanges, metacarpals, and metatarsals from tuberculous infections of other bones,<sup>4</sup> to "ballooning" of the cortex and widespread destruction of all layers of the bone. It will be seen that the primary and most extensive lesion is usually localized in the diaphysis. From the follow-up films on the patients in Group II it is seen that the normal structure of the bone is usually completely restored, and, from examination at this time, that no disability in function has resulted. In one exception, the lesion was inadequately treated during its active phase and a subluxation of the second phalanx at this time was allowed to heal uncorrected.



Fig. 3.—L. B., aged 16 years. The bones of the right hand have returned almost completely to normal; there is marked shortening of the proximal phalanx of the left hand, with resultant deformity.

*Sites of Lesions.*—Among all of the children studied, the number of bones involved in both hands and feet totaled fifty-four, twenty-eight in Group I and twenty-six in Group II. The bones of the hands were much more frequently affected than those of the feet, forty-eight in the former and six in the latter. Of the lesions in the hands, twenty-six (55 per cent) were localized in the proximal phalanx, sixteen in the metacarpals, and six in the second phalanx. No lesions were seen in the terminal phalanx of any finger or toe. The most common sites were the proximal phalanx of the index and middle fingers and metacarpals of the middle and ring fingers of the hands. There was no significant difference between the two hands, twenty-three bones of the right hand and twenty-five of the left hand being involved. Among the small bones of the feet, the proximal phalanx of toes 1, 3, and 4 were each involved once, and the

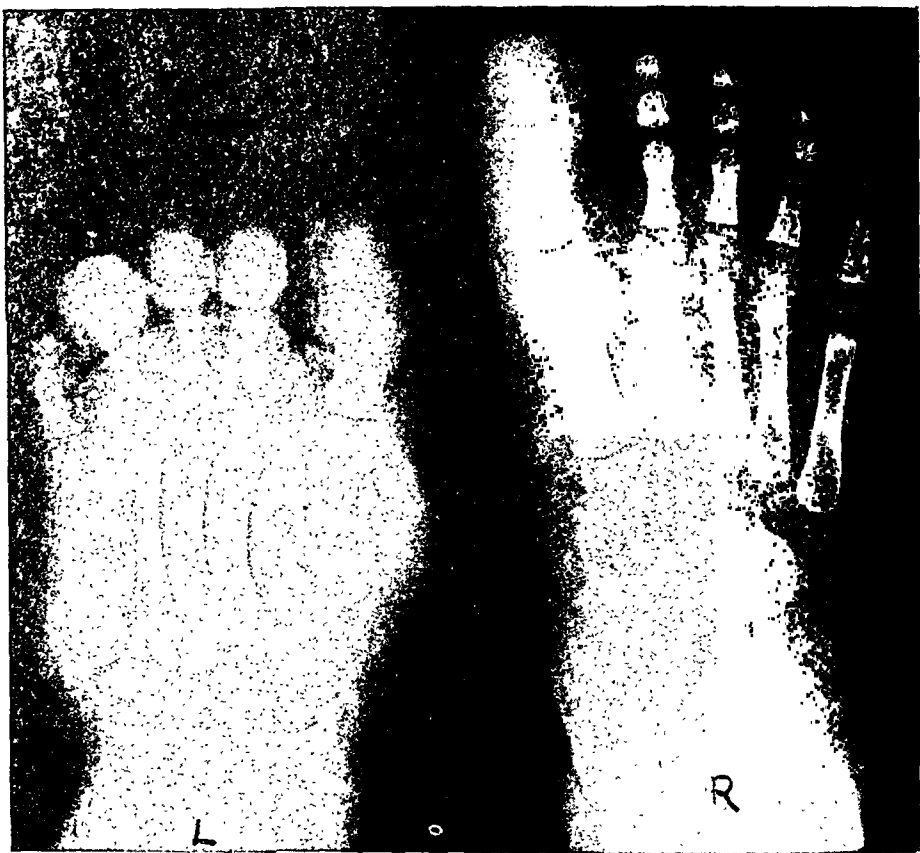


Fig. 4.—L. B., aged 2 years. Feet show destructive tuberculous lesions of first phalanx of right great toe and of the first and fifth metatarsals on the left. Note swelling of soft tissue of left foot.



Fig. 5.—L. B., aged 16 years. Feet: complete healing and restoration to normal contour has occurred in the lesions present fourteen years before, in the first phalanx, right great toe, and the fifth metacarpal left. Healing of the severe lesion, formerly present in the first metacarpal left, has been accompanied by considerable shortening of the bone and resultant deformity.



FIG. 6.—M. Y., aged 2 years. Chest film showed nonspecific root infiltration, tuberculin test positive. Destructive lesions in fifth metacarpal right, in the proximal phalanx of the second, third, and fourth digits on the right, and the third and fourth digits on the left, with marked soft tissue swelling.



FIG. 7.—M. Y., aged 28 years. The bones of the hand have returned completely to normal.





Fig. 8.—M. Y., aged 2 years Tuberculous involvement of first metatarsal, right.

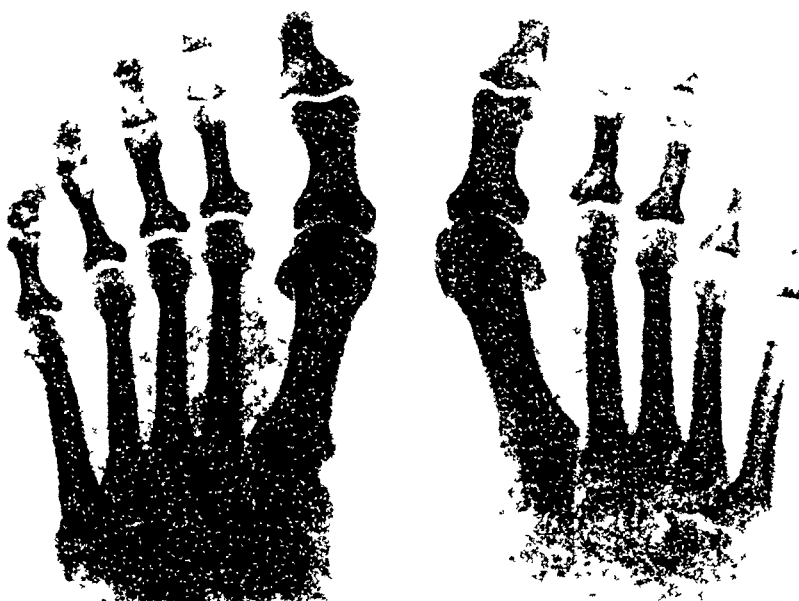


Fig. 9 —M. Y., aged 28 years. Bones of feet are now entirely normal.



Fig. 10.—M. T., aged 2 years. Mediastinal tuberculosis with phlyctenular keratitis and tuberculous lesions of the first and third metacarpals and proximal phalanx of third finger on left hand and of the proximal phalanx of the fourth finger right hand. Note periosteal reduplication.



Fig. 11.—M. T., aged 2 years. There are severely destructive lesions in the proximal phalanx of the fourth digit right hand and third digit left hand. The lesions previously seen in the metacarpals are much improved.

first metatarsal on three occasions, with a total of six lesions. Multiple lesions of the hands and feet occurred in seven patients of Group I, and five of Group II. One patient in the first group (Figs. 1 to 5) has lesions in the proximal phalanx of fingers 1, 2, 3, and 5 of his right hand, middle phalanx of finger 5 of this hand, proximal phalanx of fingers 1, 2, and 3 of his left hand, of metacarpal 4 of this hand, and of metatarsal 1 and the proximal phalanx of toe 1 of his left foot. These healed with minimal shortening of two bones (Fig. 5).



Fig. 12.—M. T., aged 8 years. The bones of the hands are normal except for slight thickening of the proximal phalanx of the right fourth and left third digits.

*Prognosis.*—With the exception of patient L. B., who is alive at present, and two patients who are presumed dead, all patients in Group I died of their tuberculous infection. In Group II all of the patients are living and in good health except for one already mentioned. Adequate serial x-rays are not available for definite statements as to time taken for healing of the dactylitis, but on the basis of three cases, mild lesions had completely disappeared within thirteen months, moderately severe ones within two years, and extensive destructive lesions within a minimum period of three years. From the histories of the patients, the lesions were found to be usually asymptomatic within eighteen to thirty-six months, provided the patients had a favorable prognosis as far as the rest of their infection was concerned and that they received adequate orthopedic care. The treatment consisted of immobilization of the affected digits in splints or casts for the period during which the lesion was active, and incision and drainage where the lesion was secondarily infected. In view of the strik-

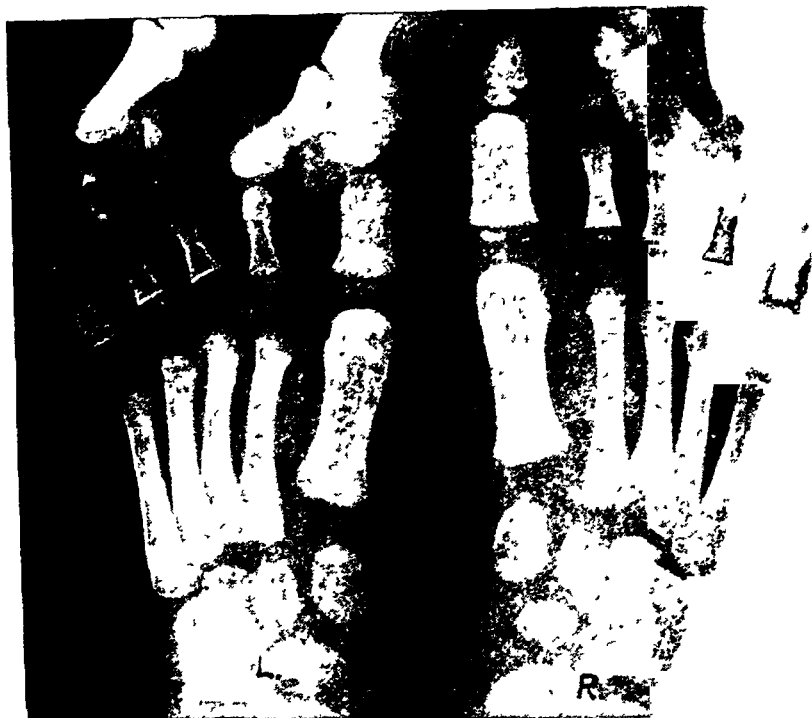


Fig. 13.—M. T., aged 2½ years. Destructive lesions in the proximal phalanges of the first and fifth toes of the right foot.



Fig. 14.—M. T., aged 5½ years. The bones of the feet have now almost returned to normal.

ing x-ray findings, it would appear that amputation or dactylectomy is definitely contraindicated. Of the four patients whose digits were amputated (and who were not included in this series), no change in the prognosis of their general condition was found; all had minimal tuberculosis.

#### DISCUSSION

Tuberculous lesions of the small bones occur with relative rarity, but this series followed in the Harriet Lane Home seems worthy of report because where the patient has survived the other manifestations of his tuberculous infection the return to normal contour and function of the diseased bones has been remarkably good.

#### SUMMARY

1. Twenty-one patients with tuberculous dactylitis complicating primary tuberculous infections in childhood were followed until death or to date (an average of eleven years).

2. Fourteen, or two-thirds of the patients, were 2 years of age or less when this complication occurred. Sixteen were negro and five were white. Eleven had dactylitis as a minor complication of a severe generalized tuberculosis, ten had dactylitis as part of a relatively mild infection.

3. The dactylitis was the presenting complaint in eleven patients.

4. The bones of the hands were involved eight times more frequently than those of the feet. The proximal phalanx of the index and middle fingers were the bones most frequently involved.

5. Provided the patient survived the other manifestations of tuberculosis, the prognosis for complete healing of the bone with return to normal contour in most instances was excellent. Healing occurred in from one to three years.

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# ACUTE GLOMERULONEPHRITIS

## A REVIEW OF NINETY CASES

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THIS report is an analysis of a series of ninety consecutive cases of children with acute glomerulonephritis at the Children's Hospital during the past three years (1943 through 1945). There were thirty-four white and fifty-six Negro patients; forty-six were male and forty-four were female. It is to be noted that there was only a slight preponderance in the number of male patients with acute glomerulonephritis in our series in contrast to the several large series reported by other authors<sup>1</sup> who found a rather noticeable predilection for males. Lyttle<sup>2</sup> in his report on 125 cases of acute nephritis in children observed a ratio nearly 2:1 for males. The average age of the ninety patients was 5.7 years; the majority were between the ages of 2 and 10 years and the youngest was 4 months of age (Table I).

TABLE I. AGE, RACE, AND SEX DISTRIBUTION IN NINETY PATIENTS WITH ACUTE GLOMERULONEPHRITIS

	NO. PATIENTS	PER CENT
<i>Age</i>		
0-1 yr.	2	2.3
1-5 yr.	36	40.0
5-12 yr.	52	57.7
<i>Race</i>		
Negro	56	62.3
White	34	37.7
<i>Sex</i>		
Male	46	51.1
Female	44	48.9

## ONSET OF CLINICAL MANIFESTATIONS

The onset of symptoms began either simultaneously with or shortly after an acute febrile disease in 86 per cent of the children in this series. A history of preceding illness was not obtained in seven cases. A hiatus of seven to fourteen days after the subsidence of the symptoms of the primary infection was most common, but several patients were admitted with an accompanying infection of the respiratory tract or skin.

The most common predisposing infections were those of the upper respiratory tract, including nasopharyngitis, tonsillitis, and otitis media; a history of such an infection was obtained for 65.3 per cent of the patients. It has been reported<sup>3</sup> that a "deep" hemolytic streptococcal infection precedes the onset of acute nephritis in about two-thirds of the patients. In our series the severity of

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the preceding upper respiratory infection appeared to be of no particular significance since many of the precipitating infections were quite mild (Table II).

Skin diseases such as secondarily infected burns, impetigo, and infected eczema form the next largest group of preceding infections (10.2 per cent). Fitcher<sup>4</sup> has recently reviewed the role of skin infections in the etiology of acute glomerulonephritis and reported the incidence to vary from 0 to 28 per cent. Scarlet fever was the cause in three patients (3.3 per cent) but may be a more common predisposing infection than this figure would indicate, for the contagion service of Children's Hospital is rather small and most persons with scarlet fever are referred elsewhere. The remaining group had a history of some other infection including pneumonia, sinusitis, mumps, cervical adenitis, and others. In three cases, two of which fall outside of the time limit of this series, acute nephritis occurred with congenital syphilis. All three patients were under 1 year of age. It is problematical whether this association between congenital syphilis and acute nephritis represents a primary invasion of the kidney by *Treponema pallidum* or a secondary involvement of the kidney resulting from the upper respiratory infection frequently found to coexist with congenital syphilis. In this regard, it is well to point out that congenital syphilis is the most common precursor of acute glomerulonephritis in infants under 1 year of age.<sup>5</sup>

TABLE II. PRECEDING INFECTIONS IN THE PRESENT SERIES OF NINETY PATIENTS WITH ACUTE GLOMERULONEPHRITIS

TYPE OF INFECTION	NO. PATIENTS	PER CENT
Upper respiratory infection (pharyngotonsillitis, otitis media)	59	65.3
Skin lesions	9	10.2
Scarlet fever	3	3.3
Mumps	2	2.2
Gastrointestinal infections	2	2.2
Pneumonia	2	2.2
Adenitis	2	2.2
Sinusitis	2	2.2
Genitourinary infections	1	1.1
Syphilis	1	1.1
Unknown	7	8.0
Total	90	100.0

Etiologic studies were not carried out on every child, but beta hemolytic streptococci were found most frequently on throat culture while *Staphylococcus aureus* was usually the organism cultured from coexisting skin infections.

#### PRESENTING SYMPTOMS

Study of the presenting symptoms in this series constitutes an interesting analysis (Table III). Edema, as might be expected, was the outstanding symptom of 59.5 per cent of the patients. Next in frequency was gross hematuria which was the chief complaint of 25.5 per cent. Abdominal pain was present at one time or another in one-third of the patients; in six, comprising 7 per cent of the total number, it was the presenting and chief complaint. In several cases the diagnosis of appendicitis was entertained upon admission; especially in those

patients with nausea and vomiting; however, this pain was usually periumbilical or located in the right upper quadrant. In several patients its origin was probably a distended, congested liver with stretching of Glisson's capsule due to heart failure. Dyspnea was occasionally noted, especially in the group with demonstrable myocardial damage, and was the main complaint of two children upon admission. Convulsions and coma were the presenting symptoms in two other patients, and in another nephritis was diagnosed by routine urinalysis after the child was admitted with a diagnosis of pneumonia.

TABLE III. PRESENTING MANIFESTATION OF ACUTE GLOMERULONEPHRITIS IN CURRENT SERIES

MANIFESTATION	NO. PATIENTS	PER CENT
Edema	54	60.0
Hematuria	23	25.6
Abdominal pain	6	6.7
Vomiting	2	2.2
Convulsions	2	2.2
Dyspnea	2	2.2
Dysuria	1	1.1
Total	90	100.0

## MAJOR MANIFESTATIONS

1. *Hematuria and Albuminuria.*—These two findings constituted the diagnostic criteria of acute glomerulonephritis and were present in every child. It is interesting to note that in at least three cases in this series, the impression of acute glomerulonephritis was entertained in view of the presence of several other manifestations of the disease, but the diagnosis was not definitely established until a second or third urine specimen revealed hematuria after twenty-four to forty-eight hours, the initial urinalysis showing no abnormalities of the urinary sediment. Red blood cells varied in amount. Gross hematuria was present in approximately one-fourth of the patients and microscopic hematuria was found in the remainder. The amount of albumin varied from 50 to 2,000 mg. per cent but the usual range was between 100 and 500 mg. per cent on initial urinalysis; the albuminuria disappeared in the majority of instances within four weeks after the onset of the initial symptoms. Casts were frequently noted. Daily examination of the urine was employed during the hospital course and reliance was placed on the correlation between the gradual disappearance of the urinary findings and the subsidence of the illness.

2. *Edema.*—Edema is the most common symptom of acute nephritis and was present in 84.4 per cent of the ninety patients in this series. It was not clinically perceptible in 16 per cent, was minimal in 37 per cent, moderate in 28 per cent, and severe in 19 per cent. The patients with nephritis without edema usually posed the diagnostic problems in this group. Edema usually developed in the face, particularly in the low tension tissues in the infraorbital region. It was often confined to this area, but frequently continued to develop and appeared in the lower extremities and subsequently in all the subcutaneous tissues, serous spaces, and viscera. The patient who develops edema of the face only to have it disappear and then reappear later on, must be regarded



as a potential candidate for classification as having subacute or chronic nephritis. It is noteworthy that in all the patients in this series who went on to recovery, the edema was either progressive or came to a standstill, and was not intermittent.

TABLE IV. FREQUENCY OF OCCURRENCE OF MAJOR MANIFESTATIONS OF NINETY PATIENTS WITH ACUTE GLOMERULONEPHRITIS

MANIFESTATION	NO. PATIENTS	PER CENT
Hematuria	90	100.0
Albuminuria	90	100.0
Edema	74	84.4
Hypertension	73	81.1
Congestive heart failure	—	57.0
Abdominal pain	35	33.3
Cerebral symptoms	28	31.1

3. *Hypertension*.—Significant elevation of the blood pressure was present in 81.1 per cent of the children in this series. Arbitrarily, in agreement with other observers, systolic pressure of 120 was selected as the dividing line for the presence or absence of *significant* hypertension, although it is recognized that in young children, particularly those under the age of 5 years, a systolic pressure of 120 may well constitute hypertension.

At least one systolic blood pressure reading above 140 was observed in 44 per cent of the patients, and pressures ranging between 120 and 140 were observed in 30 per cent. The blood pressure was usually elevated at the time of admission, although in eleven children it never did rise while under observation. One child among this group without significant hypertension died of acute, nephritic, congestive heart failure shortly after admission. In nearly all patients showing marked cardiac manifestations a significant elevation of the blood pressure was noted. Marked hypertension as a *sine qua non* in the presence of congestive heart failure associated with acute glomerulonephritis has been the subject of some discussion. It was present in all of the fourteen cases of nephritic heart failure reported by Rubin and Rapoport.<sup>6</sup> On the other hand, Levy<sup>7</sup> and Lyttle<sup>2</sup> have reported cases in which this association was not observed. In the present series, three patients with heart failure did not have significant blood pressure elevation.

Occasionally, the blood pressure was noted to rise considerably after admission, particularly in those children who were admitted to the hospital at the very onset of the illness. However, in the majority of instances the highest readings observed were at the time of admission and under treatment they fell, over a period of one to two weeks, to normalcy. The systolic pressure was found to be a reliable guide to the degree of hypertension, and in most instances the diastolic pressure followed the systolic; however, in a few cases the systolic pressure remained within relatively normal range while an elevated diastolic pressure was observed. It is probably fair to assume that if all patients with acute glomerulonephritis could be adequately followed from the very first day of their illness during the entire course, a larger percentage might show a significant hypertension.

4. *Cerebral*.—Cerebral symptoms in this disease are probably caused by vasospasm with secondary cerebral ischemia. Vasospasm is probably also the cause of the hypertension. The evidence would indicate that cerebral edema plays an unimportant role in the etiologic background of the manifestations of encephalopathy associated with acute glomerulonephritis.

Cerebral symptoms in this series were present in 31.1 per cent of the patients. All of these patients had severe headaches, convulsions, or were in coma. These three symptoms were the diagnostic criteria employed and an associated moderate or severe hypertension was usually present. In general, these symptoms indicate a severe type of acute glomerulonephritis. Some of the other patients manifested cerebral symptoms of a milder degree such as slight headaches, restlessness, and dimness of vision.

5. *Cardiac Manifestations*.—It has long been known that cardiac failure may complicate the early stages of acute glomerulonephritis. In 1879 Goodhart<sup>8</sup> called attention to this association, and since then many reports have appeared on the subject in the literature. Of particular note is Whitehill and associates<sup>9</sup> carefully studied series of 138 young adults with acute nephritis, ninety-eight, or 71 per cent, of whom showed clinical evidence of cardiac insufficiency. Forty per cent of eighty patients reported by Marcolongo<sup>10</sup> and 33 per cent of the twenty-four patients reported by Master and associates<sup>11</sup> exhibited cardiac failure. Lyttle<sup>2</sup> states that one-half of the 125 children with acute nephritis studied at Babies' Hospital in New York demonstrated cardiac failure, while fourteen of the fifty-five children with acute glomerulonephritis observed by Rubin and Rapoport<sup>6</sup> had congestive heart failure associated with the disease.

Acute glomerulonephritis has been the most common cause of congestive heart failure at Children's Hospital for the past three years, during the period covered by this series, and was present in thirty-five or 57 per cent of the sixty-two patients who were examined for evidence of this complication. The criteria used to diagnose heart failure were: (1) cardiac enlargement with congestion of the parenchyma as revealed by x-ray; (2) elevated venous pressure (using 160 mm. of normal saline as the maximal normal level) with a significant rise upon moderate pressure over the right upper quadrant; (3) engorgement with definite enlargement of the liver; and (4) miscellaneous evidence including electrocardiogram changes, pulsating cervical veins, pulmonary edema, dyspnea, and direct evidence at autopsy.

Some patients had definite evidence of cardiac dilatation by x-ray which returned to normal size while under observation, but confirmatory evidence of an elevated venous pressure and palpable liver was lacking, so these were not considered to be patients with congestive failure. However, if transient dilatation may be interpreted as evidence of partial impairment of cardiac function and these patients are grouped with those exhibiting frank congestive failure, then a total of 72.6 per cent of the sixty-two patients who were examined for evidence of this manifestation had demonstrable myocardial damage with insufficiency.

The signs of congestive heart failure were present usually in the first



Fig 1, A.

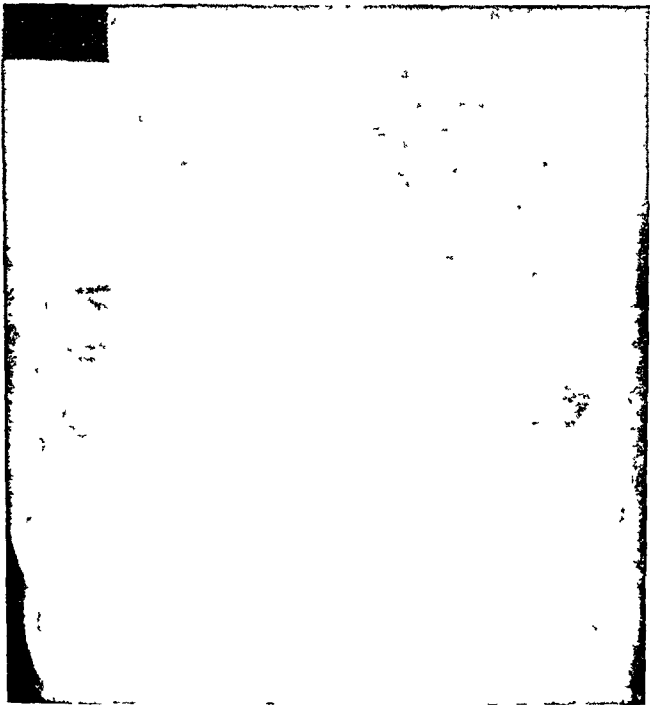


Fig 1, B.

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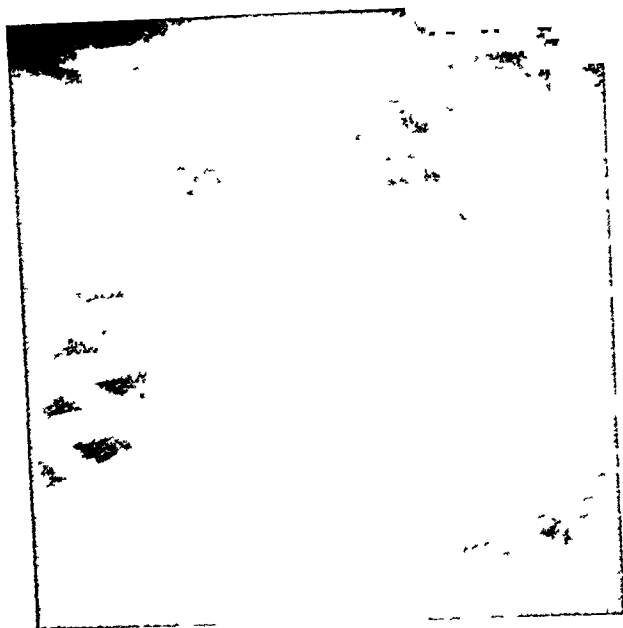


FIG. 1, C.



FIG 1, D

Fig 1.—(C K.) Serial roentgenograms of the chest demonstrating congestive heart failure associated with acute glomerulonephritis.

A, x-ray upon admission, shows the transverse diameter of the heart to be within normal limits but considerable congestion throughout the parenchyma. Venous pressure was elevated.

B, dilatation of the heart is shown on the picture taken fifty-six hours later with the congestion disappearing from the outer thirds of the lung fields. Venous pressure was still elevated. The patient was receiving digitalis.

C, further dilatation is noted on the x-ray taken four days after admission. Digitalization has been maintained, and venous pressure is normal. Congestion of the lungs is absent.

D, three weeks after admission, the heart is normal.

week after the appearance of the initial symptoms of acute glomerulonephritis. Most commonly these signs were detected upon admission; however, in several patients it was possible to demonstrate by serial roentgenograms a delay of two to three days before significant enlargement occurred.

Figs. 1 and 2 represent sets of teleoroentgenograms selected from the group showing classic evidence of congestive heart failure and illustrate the marked transient quality of decompensation due to acute glomerulonephritis.

A transient diastolic murmur at the base was observed in one patient with very severe decompensation and was interpreted as evidence of functional aortic regurgitation; this murmur disappeared when compensation occurred. Functional, apical, systolic murmurs were frequently noted but appeared to have no particular significance. Gallop rhythm was observed in five patients and is always to be regarded as a grave prognostic sign. It was present in two of the three patients who died.

The mechanism of heart failure associated with acute glomerulonephritis is not exactly known, but it is probable that there are several factors concerned with its production. The two most important of these appear to be hypertension due to vascular spasm, and toxic changes in the myocardium probably vascular in origin but independent of hypertension. Elevation of the blood pressure may represent a trigger mechanism which tips over a damaged heart into congestive failure. While the vast majority of patients showing congestive

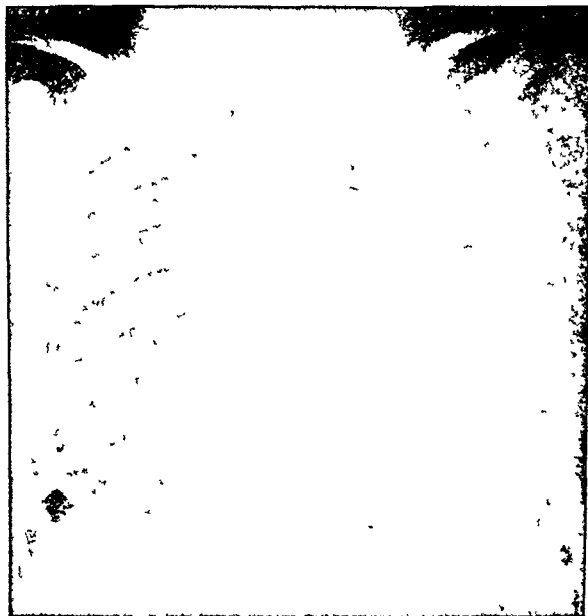


Fig. 2, A.

Fig. 2.—(S. S) Serial roentgenograms of the chest.

A, Cardiac dilatation with parenchymal congestion especially marked on the left side. The venous pressure was very high and the patient was digitalized.

B, X-ray taken three days later showing a clearing of the lung fields with cardiac dilatation. The venous pressure was still slightly elevated.

C, Sixteen days after the first x-ray was taken, demonstrating a normal heart contour.



FIG 2, B.



Fig. 2, C.

(For legend, see opposite page.)

heart failure had an associated elevation of blood pressure (95 per cent), it is worth while to note that three failed to demonstrate any significant elevation of pressure. One of these three died of congestive heart failure with a blood pressure of 110/55. Although the absence of hypertension in the presence of congestive heart failure associated with acute glomerulonephritis is relatively infrequent, the finding of even a few cases would suggest the importance of the role of underlying myocardial damage. The nature of this factor is not clearly understood. The theory that the disease represents a toxic, generalized capillaritis of the entire vascular system including the myocardium with associated temporary damage is still accepted by most observers at the present time. Longcope and associates<sup>12</sup> have pointed out the intimate relationship existing between infections due to hemolytic streptococci and the subsequent onset of acute nephritis. The association of cardiac damage with streptococcal infections is well known. Brody and Smith<sup>13</sup> found heart lesions of varying degrees of severity at autopsy in more than 90 per cent of the patients with scarlet fever and related streptococcal infections. While the common myocardial lesions described in scarlet fever appear to be of an inflammatory nature, changes noted in the cardiac muscle of patients who died of acute hemorrhagic nephritis appear to be of a degenerative character. It has been suggested by Rubin and Rapoport<sup>6</sup> that if the renal lesion in acute hemorrhagic nephritis is anaphylactoid, it is possible that the cardiac involvement may be of a similar etiology.



Fig. 3—A, Electrocardiogram taken upon admission showing inverted T waves in Lead I.  
B, Normal record noted on check-up two months later.

Electrocardiographic evidence supports the theory of actual myocardial damage. Electrocardiograms were taken at random intervals during the course of the disease in thirty of the patients in the present series, and abnormal records were found in thirteen (43 per cent). The most common abnormal changes found were the flattening or inversion of the T waves, especially  $T_1$  and  $T_2$  (Fig. 3). Follow-up studies revealed that the myocardial damage was only temporary; all of the records were normal within two to four weeks after the onset of the nephritis in those patients who had shown abnormal readings

initially. It is a fair assumption that if serial electrocardiograms had been taken in all cases, a larger percentage of abnormalities would have been recorded. Ash and associates<sup>14</sup> found significant variations in 72 per cent of fifty children with acute nephritis, by employing the serial method.

#### MINOR MANIFESTATIONS

Anemia of varying degrees of severity was a rather frequent finding, and was marked (hemoglobin 8 Gm. or less) in 20 per cent, and moderate (hemoglobin between 9 and 10 Gm.) in 52 per cent of the cases.

Anuria was not observed in any instance, but oliguria was noted not infrequently in the first few days of illness. The nonprotein nitrogen blood level was above 35 mg. per cent in 65 per cent of the cases and was normal in the remaining 35 per cent.

Fever was not characteristic of acute glomerulonephritis and was absent upon admission in 60 per cent of the cases. When an elevation of the temperature was present, an associated extranephritic infection could usually be simultaneously demonstrated.

A rapid sedimentation rate was a rather constant feature of nephritis during the acute phase of the disease.

#### PROGNOSIS AND RESULTS

Eighty-four or 93.4 per cent of the patients in this series recovered while three (3.3 per cent) died during the acute attack. Three developed chronic glomerulonephritis and one of these patients died several months later of pneumonia. All of the patients who recovered have remained well in a follow-up period varying from a few months to two years. In no case was there any residual cardiac damage demonstrable.

TABLE V. OUTCOME IN NINETY CASES OF ACUTE GLOMERULONEPHRITIS

OUTCOME	NO. PATIENTS	PER CENT
Recovered	84	93.4
Died	3	3.3
Chronic	3	3.3
Total	90	100.0

A recrudescence of the symptoms of acute glomerulonephritis, particularly hematuria and albuminuria, may be precipitated by secondary acute upper respiratory infections or by one of the common contagious diseases acquired during the convalescent period. This, however, cannot be considered as a second attack of acute glomerulonephritis but rather as an exacerbation of the original disease process, nor does such an exacerbation necessarily predicate a bad prognosis. In two such instances a recurrence of albuminuria and hematuria was noted during the convalescent period after apparent recovery; in one of these patients mumps was the complicating secondary infection and in the other, chickenpox. However, in both cases the urinary abnormalities subsided within three to four weeks and the patients went on to complete recovery.

The low incidence of chronic nephritis as a complication is in accord with several other reports. Three patients developed chronic glomerulonephritis



after an apparently acute onset, and very early in the course of their disease showed large amounts of albumin in the urine out of proportion to the number of red cells. This disproportion of albuminuria to hematuria was regarded as a significant prognostic indication of the development of chronic nephritis. The high incidence of subacute and chronic glomerulonephritis following acute glomerulonephritis reported in adults<sup>9</sup> has not been observed in this series of children.

The onset and presenting symptoms of one of the patients who went on to chronic glomerulonephritis were indistinguishable from those of patients who completely recovered. However, early in the course of the disease this child showed a gradual disappearance of red cells from the urinary sediment, associated with increasing amounts of albuminuria. At the end of a one-year follow-up period, there was still between 2,000 and 3,000 mg. per cent of albumin in the urine with but an occasional red blood cell. Symptomatically, his course has been characterized by exacerbations and remissions of generalized edema.

A second patient who went on to the chronic nephritis and subsequently came to autopsy, had a history of intermittent edema of the face for three weeks prior to admission. This patient had, upon admission, very large amounts of albumin ranging between 2,000 and 4,000 mg. per cent with relatively few red blood cells. These findings persisted until death, four months after the onset of the disease, due to an intercurrent pulmonary infection.

The persistence of albuminuria with or without hematuria for a period of one year can usually be regarded as indicative of the presence of subacute or chronic nephritis.

No definite correlation could be established between the apparent severity of the clinical picture upon admission and the ultimate prognosis. Two of the three fatal cases were thought to be only moderately ill upon admission, whereas several patients in this series presented a much more severe initial clinical picture and yet ultimately recovered.

The most common cause of death in acute glomerulonephritis in children is congestive heart failure. The three deaths in this series were the results of or were associated with this complication. However, when it is considered that 72 per cent of the patients evidenced clinical signs of myocardial involvement, the mortality rate (3.3 per cent) is relatively low.

Addis counts on the urinary sediments, erythrocyte sedimentation rates, and observation of serial urea clearance tests are valuable adjuncts during convalescence in determining the prognosis. Concentration and dilution tests, phenolsulfonphthalein excretion tests, and intravenous pyelography were employed in a few patients but were discarded as routine procedures because they provided no additional information.

#### TREATMENT

Treatment consisted of absolute bed rest until the urine was free from albumin and red blood cells. Several cases were discharged before the urinary sediment was completely normal when it was felt that the convalescence would be intelligently followed at home. When patients were permitted premature

exercise, exacerbations of albuminuria and hematuria were noted on several occasions.

A relatively high protein, high carbohydrate, low fat, salt-free diet was employed with fluids given as desired. In those cases showing a high nonprotein nitrogen, fluids were forced. High vitamin supplements were employed routinely. Blood transfusions were given only when convalescence was well advanced and the initial phase of the attack had subsided. It was thought advisable to avoid the intravenous route in a disease with acute and generalized vascular involvement such as nephritis. In two instances when blood transfusions were given during the first few days after the onset of the symptoms of nephritis, gross hematuria ensued shortly thereafter.

Sulfadiazine, sulfapyrazine, and penicillin were employed when a susceptible infection was concomitantly present, without any untoward reaction being noticed. Penicillin appears to be the drug of choice for the treatment of such coexisting extranepritic infections, since, in the presence of impaired renal function, sulfonamides may be retained with the production of an inordinately high sulfonamide blood level. Regarding the use of chemotherapeutic agents for the treatment of nephritis per se, Rapoport and associates<sup>15</sup> found no appreciable difference in comparison of a series of thirty-three patients with acute glomerulonephritis treated with sulfonamides, with a control group of forty patients who were not treated with this drug. Similarly, penicillin cannot be expected to influence significantly the course of acute glomerulonephritis.

Magnesium sulfate (0.2 c.c. per kilogram body weight of a 25 per cent solution) was given intramuscularly in those cases manifesting cerebral symptoms or in those patients who showed a rising blood pressure. This dosage was repeated every two to four hours until hypertension was under control and/or signs of cerebral encephalopathy disappeared. The intramuscular route was found adequate and in no instance was the magnesium sulfate given intravenously. It has been shown that this drug exerts its beneficial effect on hypertensive encephalopathy associated with acute glomerulonephritis due to the relaxation of the arterial spasm rather than to the production of diuresis with diminution of the degree of cerebral edema. The magnesium ion has a relaxing effect on this vasospasm.<sup>16</sup>

Surgical procedures were not contraindicated by the presence of acute glomerulonephritis when they were deemed advisable, but elective operations were deferred. Hypertonic solutions were given to several patients in an attempt to mobilize the edema without success. Mercurial diuretics were not employed because of the potential harmful effect of these drugs upon an already damaged kidney. Xanthine derivatives did not appreciably hasten diuresis in the several cases in which they were employed. Intake-output records were discarded as a tedious and unreliable procedure in children, and equally valuable information was obtained by daily weighing and observation of the resultant weight curve. Only a few of the patients in the early part of this series were digitalized; however, in the later group, the majority received digitalis for the treatment of congestive heart failure. While it is true that most patients with congestive failure due to acute nephritis will respond to bed rest alone for re-

pair of their cardiac function, it is considered advisable to digitalize all patients with decompensation because of its possible serious import. In contrast to the deleterious effect of digitalis frequently noted in patients with acute rheumatic myocarditis, no untoward reactions were noted in the group of nephritic heart failure cases who received this drug. The preparation of choice was Digifolin and one cat unit per 100 pounds of body weight were employed. One-half the total dose was administered the first day in three divided doses, then one-half of the remainder on the second day in two doses and the rest on the third day. A maintenance dose of  $\frac{1}{2}$  cat unit every day followed until evidence of heart failure had disappeared or toxic symptoms intervened.

### CONCLUSIONS

1. A review of the salient clinical features of ninety consecutive cases of patients with acute glomerulonephritis observed at the Children's Hospital during the past three years (1943 through 1945) is presented. The presenting symptoms and clinical manifestations are noted.

2. Of this series, eighty-four patients or 93.4 per cent recovered, while three (3.3 per cent) died during the acute attack. Three (3.3 per cent) developed chronic glomerulonephritis. The three deaths were associated with or were the direct result of acute nephritic congestive heart failure.

3. Acute glomerulonephritis has been the most common cause of congestive heart failure at Children's Hospital for the past three years, and was present in thirty-five or 57 per cent of the sixty-two patients with acute nephritis who were examined for evidence of this complication.

4. The treatment employed in this series is indicated and consisted largely of absolute bed rest and the management of symptoms as they appeared. The advisability of administering digitalis to all cases of acute nephritis complicated by congestive heart failure is suggested.

We wish to express our appreciation to Drs. Joseph S. Wall, E. Clarence Rice, P. A. McLondon, and Edgar Copeland for their helpful suggestions and advice. Dr. Bernard J. Walsh was the cardiac consultant and gave valuable aid and suggestions in those cases demonstrating heart complications. Dr. Charles Webb assisted in the compilation of statistics.

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# THE AGGLUTINATIVE REACTION FOR HEMOPHILUS PERTUSSIS FOLLOWING WHOOPING COUGH AND FOLLOWING IMMUNIZATION

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**N**UMEROUS attempts have been made in the past to devise a simple and reliable test for differentiating persons immune and nonimmune to pertussis. The agglutinative reaction has been compared with other tests, such as complement fixation reaction, opsonocytophagic response, mouse protection test, and skin test in rabbit and man. According to Mishulow and associates,<sup>1</sup> the high agglutinin titer observed during the active stage of whooping cough decreases rapidly with the onset of convalescence. Miller and Silverberg<sup>2</sup> and Lapin<sup>3</sup> found that the agglutinin titers were higher and persisted for a longer period following immunization than after pertussis. The response following a stimulating dose of pertussis vaccine was studied by Wu and Chu,<sup>4</sup> who noted an eight to sixty-four fold increase of the agglutinin titers one to two weeks after a booster dose given four to nineteen weeks after the last dose of the original immunization. In Lapin's series,<sup>5</sup> the agglutinin titer two weeks following a stimulating injection of pertussis vaccine showed a more than twofold increase.

Additional information concerning the degree and persistence of the agglutinin response following pertussis, after administration of various vaccines and "antigens" and after a booster dose of pertussis vaccine, are presented in this communication.

## MATERIAL AND METHODS

**Sera.**—Blood samples from 130 children (65 males and 65 females, 1 to 12 years old) attending the Pediatric Clinic were collected in sterile Pyrex centrifuge tubes, kept at room temperature for one hour, and then centrifuged at 1,500 r.p.m. for fifteen minutes. The clear serum was transferred to a sterile Pyrex test tube and stored in an ice box at 4 to 6° C. until tested, usually within one to two weeks after the withdrawal of the blood.

**Antigen.**—In preliminary tests, a commercially available, colored suspension of killed pertussis bacilli,\* diluted to a density of approximately 4 billion organisms per milliliter, was compared with a bacterial suspension prepared from phase I *Hemophilus pertussis*† and diluted to an equal density. Since the results with the two antigens were identical, the former was used in this study.

From the New York Hospital and the Department of Pediatrics, Cornell University Medical College.

Aided by a grant from The Commonwealth Fund.

\*The antigen was purchased from the manufacturer, Eli Lilly and Co.

†Obtained through the courtesy of Miss L. Mishulow of the Department of Laboratories, Health Department of New York City.

*Agglutination Reaction.*—Serial twofold dilutions, 0.5 ml. volumes in physiological saline solution of the sera, ranging from 1:5 to 1:5,120, were mixed with an equal amount of freshly diluted antigen, the final serum dilutions thus ranging from 1:10 to 1:10,240. The mixtures were made in 12 × 100 mm. test tubes, shaken by hand, and incubated overnight in a water bath at 55° C. Readings were made the next morning and the last tube in which agglutination was visible with the naked eye was recorded as the titer. If agglutination was absent or present only in a final dilution of 1:10, the result was considered negative. Agglutinations in final serum dilutions of 1:20 to 1:80 were considered as evidence for the presence of agglutinins in a "low" titer. Agglutination in dilutions of 1:160 or more were arbitrarily designated as "high" titer. The following controls were used: (1) each serum tested plus saline; (2) the bacterial suspension plus saline; (3) serial dilutions of an antipertussis rabbit immune serum plus bacterial suspension; (4) normal rabbit serum plus bacterial suspension. In every instance, control series (3) was positive; the other controls were negative. In addition, a microscopic slide agglutination reaction (Powell and Jamieson<sup>6</sup>) was carried out routinely.

#### RESULTS

*A. Children With a History of Pertussis.*—The agglutinin titer of thirty-eight children was determined one-fourth to eleven years after a history of the disease. A high titer was found in five (13.2 per cent) after an interval between disease and testing ranging from three-fourths to eight years. A low titer was present in eight (21.0 per cent), who had had pertussis one-fourth to eight years before testing. In the remaining twenty-five (65.8 per cent) the agglutination reactions were negative. These children gave a history of pertussis or of a pertussis-like disease, two to eleven years prior to testing. A graphical presentation of the results obtained in this and in the following groups is given in Fig. 1.

*B. Children Injected Prophylactically With Full Courses of Pertussis Vaccines.*—Of the forty-six children in this group, thirty-three had received the Sauer Vaccine (Parke, Davis & Co.) and the remaining thirteen had been given various other commercially available pertussis vaccines (Cutter's D-P-T, Lederle's, Lilly's, and New York City Board of Health's vaccines). Usually, a total of ninety to 100 billion killed microorganisms was administered subcutaneously, given with an interval of four weeks between the three injections. The agglutination reaction was negative in three (6.5 per cent), a low titer was noted in ten (21.8 per cent), and the remaining thirty-three (71.1 per cent) had agglutinins in high titers (Fig. 1). The time interval between the last injection and testing for agglutinins ranged from six weeks to nine years and is presented in Fig. 2.

*C. Children Injected Prophylactically With Full Courses of Pertussis Antigen.*—A full course of three subcutaneous injections of 1 c.c. (with an interval of three weeks between injections) of Tri-Immunol,\* "a bacterial vaccine made

\*Obtained through the courtesy of Lederle Laboratories, Inc.

from diphtheria toxoid, tetanus toxoid and pertussis antigen," was given to twenty-four children and their agglutinin response studied six to eighteen months later. Negative results were found in eight (33.3 per cent), a low titer in fourteen (58.4 per cent), and a high titer in two (8.3 per cent) (Fig. 1).

*D. Controls With No History of Pertussis or Prophylaxis.*—The sera of seventeen children were tested. A low agglutinin titer was found in one; the others were negative (see Fig. 1).

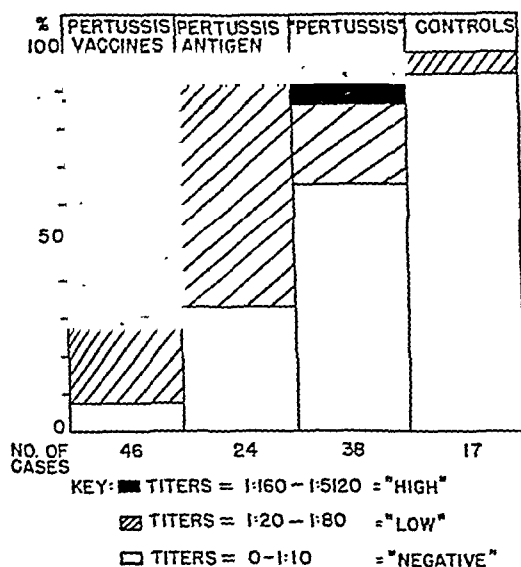


Fig. 1.

*E. Children Injected With a Stimulating Booster Dose of Pertussis Vaccine.*—Of the thirty-nine children in this group, nine gave a history of pertussis (group A), five had received pertussis vaccines (group B), and twenty-five had received pertussis antigen (group C). In five of these children, no agglutination reactions were made prior to the administration of the booster dose. The results are presented in Table I.

TABLE I. EFFECT OF "BOOSTER" INJECTION OF PERTUSSIS VACCINE ON AGGLUTININ TITER

PREVIOUS HISTORY	NUMBER	TITER* BEFORE BOOSTER INJECTION			INTERVAL BETWEEN BOOSTER AND AGGLUTININ TEST (WEEKS)	TITER* AFTER BOOSTER INJECTION		
		NEGATIVE	LOW	HIGH		NEGATIVE	LOW	HIGH
Pertussis	9	7	2	0	6-10	0	5	4
Vaccine injections	5	3	1	1	6-20	1	0	4
Antigen injections	20	7	11	2	4-16	0	5	15
Antigen injections	5	not tested			8-12	0	2	3

\*Number of sera that were negative or had a low or high agglutinin titer.

*F. Comparison of Slide Agglutination With Test Tube Agglutination.*—The slide and test tube agglutination reactions were compared in 191 experi-

ments. The results are summarized in Table II. They show that the slide agglutination method alone may not differentiate between low and high agglutinin titers.

TABLE II. COMPARISON OF AGGLUTININ TITERS OBTAINED BY SLIDE AGGLUTINATION WITH THOSE OBTAINED BY TEST TUBE AGGLUTINATION

SLIDE AGGLUTINATION	NUMBER	NUMBER OF SERA IN TEST TUBE AGGLUTINATION		
		WITH NEGATIVE TITER (0-10)	WITH LOW TITER (20-80)	WITH HIGH TITER (160 OR MORE)
Negative or doubtful	73	53	20	0
Weakly positive	33	0	23	10
Moderately positive	63	0	21	42
Strongly positive	22	0	0	22
Total	191	53	64	74

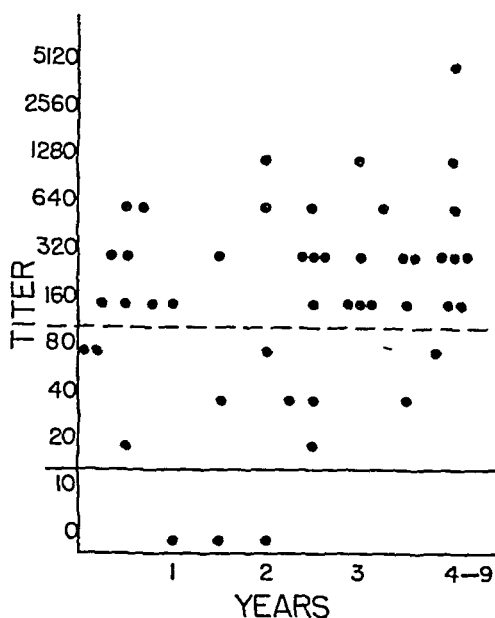


Fig. 2.

#### DISCUSSION

Our results indicate that agglutinins for *H. pertussis* can be detected in the serum of approximately one-third of the patients (34.2 per cent) for as long as eight years following the disease. This low incidence of positive response may be due in part to the difficulty of differentiating between true *H. pertussis* and *H. parapertussis* infection from the history, but in any case it would appear that the agglutinative reaction is of limited value in determining the state of immunity of an individual who allegedly had pertussis.

On the other hand, prophylactic injections with *pertussis vaccines* were followed by the appearance of agglutinins in forty-three of forty-six instances (93.5 per cent), and in thirty-three the titers were high and remained high for years, the longest observation being nine years postimmunization. Of the three

children who had no agglutinins, two had been given prophylaxis by their own physicians. All three were given stimulating injections, and two developed agglutinins in a high titer, while the third did not. This was the only failure in the group, and is unexplained.

In contrast to the consistently positive results in the vaccine group, of twenty-four children injected with "antigen," only two developed agglutinins in high titer; but Tri-immunol contains only a pertussis antigen obtained "after removal of the bacteria in the Sharples centrifuge and separation of the filtrate in the Berkefeld filter." Therefore, little if any agglutinin production should be expected in this group. The high titers observed in two children may be explained by the fact that the antigen might have contained sufficient antigenic components of *H. pertussis* bacilli to elicit an occasional marked agglutinin response, or by an anamnestic reaction to an undiagnosed pertussis infection in the past.

As far as we were able to ascertain, only two cases of pertussis occurred among those children of this study who received prophylaxis. They were siblings. One had received vaccine injections by his own physician but did not develop antibodies. A stimulating booster dose of vaccine was given to this child in our clinic but it also failed to elicit agglutinins (this was the only failure previously mentioned). The second child had been given pertussis antigen and had developed agglutinins in a low titer (1:80); a stimulating booster dose of vaccine raised the agglutinin titer slightly (from 1:80 to 1:160). The data are, therefore, inadequate to correlate agglutinin production with the state of immunity. However, our immunologic results may be compared with interesting clinical observations recently published by Cravitz and Cauley. These authors found that only 9.2 per cent of exposed Sauer-immunized children contracted pertussis, while 67.2 per cent of those who had received prophylaxis with the Lederle Detoxified Pertussis Antigen contracted pertussis upon exposure. Since the antigen used for prophylaxis in group C of this study was presumably identical to the one used by Cravitz and Cauley, the combined evidence suggests that bacterial vaccines confer high agglutinin titers and immunity, while administration of "antigens" does not. The presence of agglutinins in immunized persons may thus signify the existence of immunity to pertussis as suggested previously by Miller and associates.<sup>5</sup>

Stimulation of the antibody production by a single booster dose of a potent vaccine was successful in thirty-three of thirty-four attempts. The titers of seventeen children were negative at the time the booster dose was given. After the stimulating injection, low titers were found in seven, and high titers in nine children (one child's titer remained negative, as previously mentioned). The titers of fourteen children were low at the time the booster dose was given. They rose from 1:20 or 1:40 to 1:80 in three instances, and to high titers in the other eleven children (three to sixty-four-fold increases). Twofold to fourfold increases of the titers were found in three children who had high titers at the time of injection with the booster dose.



## SUMMARY AND CONCLUSIONS

1. The agglutinative reaction for *H. pertussis* was found to be positive in 34.2 per cent of children who had a history of pertussis. The longest interval between recovery from the disease and testing with positive result was eight years.

2. Following prophylaxis with bacterial vaccines, agglutinins were found in 93.5 per cent; some of the determinations were made as long as nine years after immunization.

3. Prophylactic injections of "pertussis antigen" were rarely followed by high agglutinin titers.

4. Stimulating injections of pertussis vaccines evoked a notable rise of circulating agglutinins in 97.4 per cent.

5. There was some correlation between the results obtained by slide agglutination and test tube agglutination, but the slide test alone did not always differentiate between low and high agglutinin titers.

6. Of seventeen untreated control patients, sixteen had no agglutinins and one had agglutinins in low titer.

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# INTRAVENTRICULAR BLOCK IN MALNUTRITION AND VITAMIN B DEFICIENCY

## A REPORT OF TWO CASES IN CHILDREN

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**E**LECTROCARDIOGRAPHIC changes due to vitamin B deficiency have been repeatedly described in recent years. Weiss and Wilkins,<sup>12</sup> in an extensive study on vitamin B<sub>1</sub> deficiency, found the most common changes to be depression and inversion of T waves and prolongation of the electrical systole. At times, low voltage of the ventricular complexes and premature beats were found. Similar electrocardiographic alterations in vitamin B<sub>1</sub> deficiency have been reported by other authors.<sup>1, 4, 5, 7</sup> The administration of thiamine chloride resulted in abolition of these electrocardiographic abnormalities. Changes in the electrocardiogram have also been described in pellagra. The abnormalities in pellagra are similar to those found in B<sub>1</sub> deficiency, and consist mainly in alterations of the T waves and the S-T segment.<sup>2, 8</sup> These changes are due specifically to niacin deficiency, since they disappear rapidly after treatment with niacin.<sup>11</sup>

In this paper, two cases of malnutrition and vitamin B deficiency are reported in children in whom an intraventricular block was found at the height of the deficiency and disappeared after treatment.

**CASE 1.**—A 15-month-old boy was admitted to the Pediatric Department B on July 5, 1943, because of severe diarrhea and vomiting lasting a week. The child had always been poorly fed and had had diarrhea on previous occasions. On admission, he was markedly undernourished, and his weight was 6.300 kilograms (normal average, 11.000 kilograms). He was conscious but apathetic and did not react to his surroundings. Distinct signs of dehydration such as sunken eyeballs and plastic skin were present. The gums were red and swollen, the tongue was smooth and atrophic, the heart sounds were feeble. There were no abnormal findings in the lungs and abdominal viscera. During the first two days of his stay in the hospital there was no vomiting and no diarrhea. On July 7 diarrhea and vomiting recurred, and the child showed signs of acute dehydration and acidosis. An intravenous drip infusion of normal saline and 5 per cent glucose was installed. In addition, the child received daily 10 mg. thiamine chloride, 50 mg. niacin and one ampule of liver extract. The patient was also given a course of sulfathiazole by mouth since the diarrhea was considered to be of infectious origin. The intravenous infusion was discontinued after three days but medication with vitamins and sulfathiazole was continued. Later the child became more responsive and a general improvement gradually took place.

**Electrocardiographic Examinations.**—On July 6, the day following admission, the first electrocardiogram was taken, which showed the following changes: normal sinus rhythm; frequency, 80, P-R interval 0.2 sec., width of the ventricular complexes in the first lead 0.10 sec., in the second 0.20 sec., and in the third 0.20 sec. T waves were absent in the three limb leads (Fig. 1, A). On July 15 after nine days of treatment a second electrocardiogram was taken with the following results: normal sinus rhythm, frequency 88, right axis shift, P-R interval 0.17 sec. The width of the ventricular complexes was normal. T waves in the first and third lead were upright, in the second lead, isoelectric (Fig. 1, B).

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Thus we have before us a case of malnutrition and vitamin B deficiency with severe electrocardiograph changes and intraventricular block, which disappeared following a short course of treatment with vitamin B<sub>1</sub>, niacin, and liver extract.

CASE 2.—A 5-year-old girl was admitted for the first time to the Pediatric Department A on July 3, 1945, suffering from severe diarrhea of three weeks duration. There was nothing of importance in her past or family history. On admission the child was markedly undernourished, her weight was 11.700 kilograms (normal average, 18.000 kilograms). There were no pathologic findings in the heart and lungs. The child had severe atrophic glossitis and edema of both legs. The stool was liquid and did not contain any parasites. The blood count was as follows: red blood cells, 3,550,000; hemoglobin, 60 per cent (Sahli), white blood cells, 6,500, with a normal differential count; total blood protein,

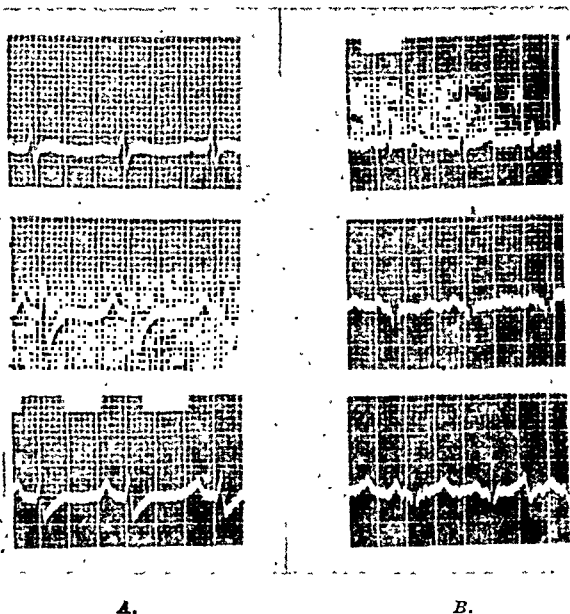


Fig. 1.—A, first electrocardiogram on July 6, 1943, showing widened ventricular complexes and absent T waves. B, After nine days of treatment with vitamin B, niacin, and liver extract, the electrocardiogram is normal.

3.00 Gm. per cent; and albumin, 1.60 Gm. per cent. An intestinal infection was suspected and sulfaguanidine was given. The child received a diet rich in protein (protein milk), yeast tablets, and two blood transfusions. With treatment diarrhea gradually subsided and the general condition improved. The edema disappeared and on July 16 blood total protein went up to 6.1 Gm. per cent, and albumin to 4.05 Gm. per cent. On Aug. 9, 1945, the child was discharged in a good general condition. On Aug. 21 she was readmitted because of recurrence of the diarrhea. Again she was in a state of malnutrition (weight 11.350 kilograms), but this time no edema was noted. The tongue was smooth and fiery red. The total protein of the blood was 5.5 Gm. per cent. A course of sulfaguanidine was given again as well as yeast tablets and small amounts of niacin. On August 23, 165 c.c. of plasma were transfused. The treatment with yeast tablets was continued for three days, after which the child received niacin only (from August 21 to August 28, a total of 650 mg. niacin was given). Only slight improvement followed this treatment, and malnutrition was still present. A general and more comprehensive treatment consisting of liver extract, blood transfusion, vitamins, and concentrated diet was therefore instituted, resulting in gradual improvement in the patient's condition.

**Electrocardiographic Examinations.**—On the patient's first admission an electrocardiogram was made, which revealed isoelectric T waves in the first and second lead. During the second stay in the hospital three electrocardiograms were taken, between August 21 and August 28. The first showed the following: normal sinus rhythm, frequency 110, P-R interval 0.23 second (A-V block, first degree), widened ventricular complexes in the three leads (in the first lead 0.14 second, in the third lead 0.11 second; in the second lead the exact width could not be determined). T waves were undifferentiated in the three limb leads. This tracing resembled a right intraventricular block (Fig. 2, *A*). A second electrocardiogram taken on August 23 showed the same findings. A third electrocardiogram was taken on August 28. This was normal except for moderately low voltage of the ventricular complexes (Fig. 2, *B*).

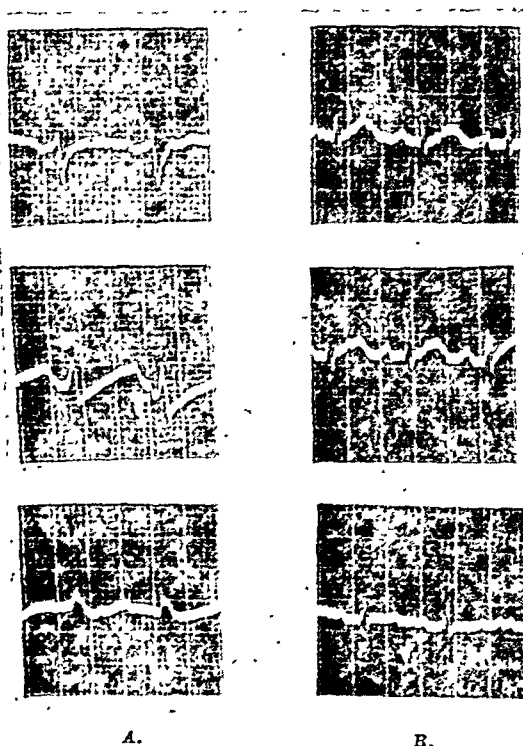


Fig. 2.—*A*, electrocardiogram on July 21 and July 23, 1945, shows prolongation of the P-R interval, widened ventricular complexes and absent T waves. *B*, electrocardiogram on July 28, after treatment with niacin only, is normal.

The electrocardiograph changes in this case were similar to those observed in the first one, the outstanding alterations being a prolongation in the intraventricular conduction time and abnormal T waves. All these changes disappeared completely after five days of treatment with niacin.

#### COMMENT

Both cases represent examples of reversible intraventricular block. This condition is rare and may be encountered in cases of acute heart failure, acute coronary insufficiency, acute infections, diphtheria, and digitalis overdosage. All these etiological factors could be excluded in our cases. Both patients had been suffering from prolonged diarrhea and were poorly fed. The clinical examination in both cases revealed, besides malnutrition, distinct evidence of

vitamin B deficiency (glossitis). In the first case the improvement in the electrocardiogram took place nine days after commencement of treatment with vitamin B<sub>1</sub>, niacin, and liver extract, at which time the general condition of malnutrition was not yet affected. In the second case the disappearance of the electrocardiographic abnormalities was observed after five days of treatment with niacin only. It seems, therefore, that the vitamin deficiency was mainly responsible for the unusual and marked electrocardiographic abnormalities.

The changes described hitherto in human vitamin B deficiency were especially concerned with the T waves, which were flattened, isoelectric, or inverted. In vitamin B<sub>1</sub> as well as in niacin deficiency they were regarded as due to disturbed intracellular metabolism. The question arises as to whether such a marked change as an intraventricular block may be of metabolic origin, or whether it is caused by organic changes in the myocardium. It is generally accepted today that a deficiency state develops by stages. After the tissues become depleted of the specific nutrient, metabolic defects appear, and finally structural changes take place. Diffuse, isolated myocarditis associated with dietary deficiency has recently been described by Toreson.<sup>10</sup> The electrocardiogram in his case showed low and widened ventricular complexes. On autopsy, dilatation and hypertrophy of the heart and chronic, noninfective, inflammatory lesions of the myocardium were found. In animal experiments, focal and diffuse necrosis of the myocardium have been observed in pigs dying of thiamine deficiency.<sup>3</sup> Similar histologic changes have been noted by Hundley and associates<sup>6</sup> in rats chronically deficient in thiamine. These authors observed, besides other electrocardiographic changes, transient bundle branch block. In this study it was found that there was no conformity between the electrocardiographic changes and the pathologic findings. From previous observations<sup>10</sup> it appears that reversible electrocardiographic changes in pellagra were more marked in younger persons. The myocardium of young people seems to be more sensitive to metabolic disturbances than the myocardium of older individuals. May<sup>9</sup> made similar observations in studying the effect of anoxemia upon normal subjects. He reported that the degree of T-wave flattening was very high in young subjects and diminished greatly with advancing age. The rapid improvement of the electrocardiogram in our cases suggests that the abnormalities were due to metabolic disturbances affecting the intraventricular conductive system.

#### SUMMARY

In two children suffering from malnutrition and vitamin B deficiency, intraventricular block and abnormalities of the terminal deflection which disappeared following vitamin treatment were observed. The first patient received niacin, thiamine and liver extract, while niacin only was given to the second. These observations suggest that reversible intraventricular block may be caused by deficiency of the vitamin B complex.

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## STREPTOMYCIN TREATMENT OF SALMONELLA ENTERITIS IN INFANTS

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EARLY observations by Waksman<sup>1</sup> and collaborators on the antibiotic action of streptomycin revealed the genus *Salmonella* to be one of the susceptible gram-negative organisms. Subsequent in vitro, in vivo,<sup>2</sup> and clinical<sup>3</sup> studies of the nature and activity of streptomycin repeatedly demonstrated its inhibitory effect on various *Salmonella* strains. An in vitro investigation of particular interest is the work of West and associates<sup>4</sup> who tested the susceptibility to streptomycin of 412 cultures of *Salmonella*, including all of the then known 154 serologic types, and found them to be inhibited in concentrations ranging from 2 to 23 units per milliliter. In view of the cases reported here it may be noted that these investigators found *Salmonella typhimurium* to be among the more susceptible strains.

We have recently had opportunity to observe several cases of *S. typhimurium* enteritis in the newborn.\* This type of gastrointestinal infection is a more frequent cause of infantile diarrhea than is commonly believed. Though there are few comprehensive studies in the literature of *Salmonella* infections in infants, the observations recorded in recent large series of all age groups indicate that *Salmonella* gastroenteritis and its complications are an important pediatric problem. Thus, in analyzing 2,000 cases of human *Salmonella* infection, Seligmann and associates<sup>5</sup> report the occurrence of 17 per cent in infants and 40 per cent in children under 10 years of age. In this series as in a previous one of 1,000 cases,<sup>6</sup> the authors observed that the organism most commonly isolated was *S. typhimurium*, which occurred in more than 30 per cent of the infections reported.

Though the *S. typhimurium* usually remains restricted to the gastrointestinal tract, resulting in a mild diarrhea which is self-limited, fatalities due to secondary invasion producing septicemia, pneumonia, and meningitis, do occur. One outbreak involving seventeen infants with six deaths has been reported.<sup>7</sup> In view of the known streptomycin susceptibility of the organism and the possibility of preventing secondary invasion, it was decided to use streptomycin in treating five cases here reported.

### CASE REPORTS

CASE 1.—B. H., a full-term male infant, was delivered by low forceps on May 16, 1946. There were no abnormal physical findings and the infant was fed a routine evaporated milk formula. During the first two days of life, meconium and apparently normal brown stools were passed. On the third day there was a sudden rise in temperature to 104° F.,

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The Streptomycin used in this study was supplied through the courtesy of Dr. Chester S. Keefer of the National Research Council, Committee of Chemotherapeutics and other agents.

\*The epidemiology of this outbreak will be reported elsewhere.

associated with a diarrhea of eight green, mucoid stools in twenty-four hours. Supportive clyses were given and the feeding was changed to a low caloric, fat-free, protein milk formula. Temperature was normal on the following day and remained so during the entire course. There was no evidence of systemic involvement.

The stools were less frequent although still green and mucoid on the second day of illness. Stool cultures revealed infection with *S. typhimurium*. On the fifth day, streptomycin became available and was administered orally in 25 mg. doses every three hours for three days (total, 600 mg.). During the first day of therapy, stool culture was positive for the infecting organism, but on the second and third day the stool was sterile and the pathogenic as well as the fecal flora had been inhibited. However, on the day following cessation of therapy the stool was again positive for *S. typhimurium*. Infected stools persisted for three days when another course of therapy was instituted with an increase of oral dosage to 50 mg. every three hours for three days (total, 1,200 mg.). The stools were sterile during the first and second day of therapy on this dosage, and on the third day the pathogen could not be cultured from the stool though the normal fecal flora had returned.

The infant was now on an evaporated milk formula and the stools, although yellowish green, were of good consistency and frequency. To prevent cross contamination the infant was discharged but stools were received from home for culture. On the sixth day after discharge, stools were again positive for *S. typhimurium*. Three additional specimens taken over the following six days revealed a carrier state of *S. typhimurium*.

CASE 2.—F. P., a full-term male infant, was delivered by Barton and Simpson forceps on May 12, 1946. The immediate postnatal course was uneventful. On the third day of life eight green, mucoid stools were passed and the temperature rose to 104° F. The infant was starved for eight hours and a low caloric, fat-free, protein milk formula was fed. Adjuvant clyses were given. The temperature hovered between 101 and 102° F. for four days and the stools, although less frequent (four to five per day), were green and mucoid. Stool cultures on the third and fourth day after onset were positive for *S. typhimurium*. On the eighth day, 25 mg. of streptomycin were given orally, and repeated every three hours for three days (total dose, 600 mg.). On the second day of therapy the stool was sterile. However, four days after therapy was terminated the infecting organism had reappeared in the stool. Stool cultures remained positive for eight days thereafter at which time another course of treatment with dosage increased to 100 mg. of streptomycin orally every three hours for two days was begun (total, 1,600 mg.). On the second day of therapy the stool was sterile. The infant was discharged. Culture of a stool brought from home six days after the last dose of Streptomycin revealed the normal fecal flora. However, two days later *S. typhimurium* was again recovered from the stool. Specimens received on alternate days for a week continued to reveal the infecting organism.

CASE 3.—R. E., a full-term, normal infant, was delivered spontaneously on May 17, 1946. Physical examination was negative. The infant was breast fed. On the third day of life there was an unexplained rise of temperature to 101° F. which persisted for forty-eight hours. The stools were yellowish green but only three per day and of good consistency. In view of the existing outbreak, the stool was cultured and found to be infected with *S. typhimurium*. The infant was fed a diluted evaporated milk formula. There was no evidence of systemic illness. Streptomycin was administered orally 50 mg. every three hours for three days (total, 1,200 mg.). Stools cultured during the three days of medication as well as two days after the last dose were all sterile, and the infant appeared to be thriving. On the fifth day after the last dose of streptomycin, the stools became watery and frequent (nine in twenty-four hours) and culture revealed the recurrence of the infecting organism.

The infant continued to have a moderately severe diarrhea with positive stools for five days, at which time streptomycin again became available, and was administered orally in 50 mg. doses as well as intramuscularly in 25 mg. doses every three hours for three days (total, 1,800 mg.). After twenty-four hours of this combined oral and parenteral therapy there was no marked improvement and it became necessary to starve the infant for twenty-four hours



and administer intravenous fluids followed by feeding of gradually increasing amounts of fat-free, protein milk. The diarrhea subsided. On the third day of this combined therapy the stool was sterile, and remained so during the twenty-four hours after medication. The next day the normal fecal flora had returned. However, five days after medication the stool was again positive and remained so for three successive days.

CASE 4.—J. K., a full-term, normal, male infant, was delivered by Barton forceps on May 11, 1946. Examination revealed a left hydrocele and undescended testicle. On the second day of life the temperature rose to 102° F. There were no clinical findings. The temperature fluctuated between 102° and 103° F. on the following two days, and the stools were green, mucoid, and increasing in frequency (six in twenty-four hours). On the sixth day the temperature was normal and remained so but *S. typhimurium* was recovered from the stool. The infant was fed gradually increasing amounts of fat-free, protein milk and adjuvant clyses were given. The stools decreased in number (three to four per day) but continued to be green and mucoid. There were no evidences of systemic illnesses.

Until this time the infant had received no streptomycin as a control. Stools continued to be positive on the seventh, eleventh, fourteenth, fifteenth, and seventeenth days, at which time it was decided to institute therapy. Streptomycin was given orally in 50 mg. doses every three hours for three days (total 1,200 mg.). During the second and third day of therapy, stools were sterile. On the day after therapy, *S. typhimurium* reappeared in the stool. The infant was discharged on the twenty-third day. Stools from home cultured on alternate days for a period of one week continued to reveal the infecting organism.

CASE 5.—J. P., a normal, full-term, female infant, was delivered spontaneously on May 14, 1946. On the third day of life there were three, loose, watery stools associated with a temperature of 102° F. On the following day the temperature was normal although stools continued to be loose and frequent (eight in twenty-four hours). Stool culture revealed *S. typhimurium*. There was no evidence of systemic involvement. The infant was fed a gradually increasing fat-free, protein milk formula and adjuvant clyses were given.

This case remained untreated for two weeks and served as another control. Positive stool cultures were reported on the eighth, eleventh, fourteenth, sixteenth, seventeenth, eighteenth, and nineteenth days. On the nineteenth and twentieth days, streptomycin was given orally in 100 mg. doses every three hours (total 1,600 mg.). The stool was sterile on the second day of therapy as well as during the following twenty-four hours. Forty-eight hours later the pathogen recurred in the stool. The infant was discharged on the twenty-fourth day. Stools received from home on alternate days for one week following discharge were positive for *S. typhimurium*.

#### BACTERIOLOGY

The bacteriologic stool examination consisted of direct plating of the material on SS and Endo agar plates and seeding in Kauffmann's tetrathionate medium with subculture on SS plates after eighteen hours of incubation. Suggestive colonies were picked up for cultural and serologic tests. Identification of culturally typical cultures was performed by the use of group-specific O-sera and type-specific H-sera. In about 50 per cent of the specimens the suspected organism could be isolated from direct platings.

Studies on streptomycin activity against *Salmonella* organisms were begun in the bacteriologic laboratory of this hospital some months before the described outbreak occurred. M. Wassermann and one of us (E. S.), performed animal experiments and tested a great many different *Salmonella* cultures for their sensitivity to streptomycin in the test tube. Detailed results will be reported elsewhere. Of forty-one freshly isolated strains of *S. typhimurium*,



and urine, for most is excreted unchanged in the feces in amounts more than enough to suppress susceptible organisms.<sup>8</sup> On the other hand, following parenteral administration, 40 per cent to 87 per cent of the drug is excreted in the urine within twenty-four hours; little, if any, is excreted in the feces.<sup>9, 10</sup> Inasmuch as in the five cases reported here we were dealing with an infection apparently limited to the gastrointestinal tract, the oral route appeared indicated.

Results as presented on Chart I reveal a distinct bacteriostatic action following oral administration of streptomycin. The effect, however, was only temporary. During and shortly after the ingestion of the drug, the pathogen as well as the normal flora were inhibited, resulting in sterile stools. However, in most instances within forty-eight hours, the pathogen, as well as the normal flora, reappeared. Repeating the treatment or increasing the dose again resulted only in temporary bacterial suppression. Inasmuch as not all stools were cultured daily, it is not always possible to state accurately the time interval between cessation of therapy and reappearance of the normal flora and the pathogen. Usually, stools remained sterile on culture for one to two days, after which normal growth was observed. *S. typhimurium* sometimes recurred twenty-four hours after the termination of medication; in other instances it reappeared from two to ten days later. There seemed to be no relationship between the total amount of ingested streptomycin and the time of reappearance of the pathogen.

In no instance did there seem to be any evidences of drug toxicity, even with doses as high as 800 mg. of streptomycin daily (Cases 2 and 5). Due to the limited supply of the drug, it was not possible to observe the effect of even larger doses over a longer period of time. However, the course of Case 3 merits added attention. The stools of this infant were rendered sterile for five days, beginning with the first day of the initial course of 400 mg. daily. This was the most pronounced bacteriostatic effect in the series, but the recurrence of the pathogen after the fifth day coincided with diarrhea of a more serious nature than that of the initial infection. A possible explanation is the recurrence of the infecting organism in the gastro intestinal tract at a time when the normal flora had not yet returned, allowing for a more rapid growth of the pathogen, and an increased toxic action.

The clinical effect of the therapy in these five cases cannot be judged conclusively. The general symptoms were mild and did not differ materially from those in the control cases. No systemic generalization of the infection took place.

In animals, the clinical effect consisted only of the postponement of the final, often fatal, outcome. In human beings, with a generally milder infection, this delay of pathogenic action may have therapeutic value. The action of streptomycin might secure a safety zone until the patient is able to build up his own biologic defense. Prolonged treatment would probably suppress toxic action at least temporarily and thereby spare infants added hazards in the most labile time of their life. This, of course, is mere conjecture; but it gives the warrant for further therapeutic studies in this field.

## SUMMARY

1. Five infants infected with *S. typhimurium*, were treated with streptomycin; four of them by oral administration only, one with combined oral and parenteral therapy.

2. The clinical course of the infection was rather mild in the treated and untreated infants. The effect on the symptoms of the disease could not be appraised.

3. Doses from 25 to 100 mg. orally given at intervals of three hours succeeded in suppressing the growth of the normal fecal bacteria as well as the pathogenic organism.

4. Discontinuance of treatment resulted in quick reappearance of *S. typhimurium* and the normal fecal flora.

5. Salmonella organisms isolated after the end of treatment showed no increased streptomycin resistance.

6. Almost identical results were obtained in animal experiments.

7. The possible therapeutic value of the limited bacteriostatic effect of streptomycin in salmonellosis is discussed.

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## DEVELOPMENTAL PEDIATRICS

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**P**EDIATRICS is unique among the specialties of clinical medicine. Other specialties are focused upon a single organ system or some one aspect of the human organism, while pediatrics is focused upon the early sectors of the life cycle and remains a form of general medicine concerned with the total child. It derives its strength and also a distinctive social significance from this kind of specialization.

Whatever social legislation the future may hold, the inherent technologic trends in medicine will lead to a mobilization of diagnostic and supervisory resources at the beginnings of the life cycle. By necessity as well as by tradition, pediatrics holds the most strategic position in the whole scheme of preventive and constructive medicine, since health protection begins with the beginning of life and growth.

The first task is to insure survival of the newborn infant. The second task is to safeguard his optimal growth. By this simple logic, development as well as disease falls within the province of clinical pediatrics. The present paper attempts to indicate how the diagnosis and supervision of infant development may be more fully incorporated into the arrangements of pediatric medicine, both at the level of the practitioner and at hospital and health centers.

### THE CONCEPT OF DEVELOPMENT

The concepts of development and disease cannot, of course, be divorced. In many diseases it is the developmental consequences which are of critical concern. The severity and the incidence of disease are influenced by age and maturity. The vast field of allergy and immunity involves developmental factors at every turn. Many abnormal and atypical modes of development must be interpreted in terms of disease. In cases of blindness and deafness and of sensorimotor impairment, the effects upon the course of development are of supreme importance. Even malnutrition may lead to maldevelopment. Indeed, health may be here defined as that optimal condition of a growing organism which denotes and fosters a maximum of development.

For such reasons, the practitioner never escapes problems of development, whether he is "merely" supervising the nutrition of a well baby or following the growth career of a chronically sick, handicapped, or defective child. All children, normal or abnormal, are confronted by the universal problem of growing up, and the parents who make up our society are looking first of all to medical science for help in the complex task of rearing their children.

To be sure, there are many parents who are overanxious, and who, in a shallow, emotional way, are overconcerned about the psychology of their young offspring. They think in terms of conditioned reflexes and subconscious complexes, and they use foreboding psychoanalytic phrases to give voice to their

worries and misinterpretations. There is a good deal of sophisticated superstition due to misleading popular education. The widespread breakdown of wholesome family life has added to confusion and insecurity. This simply heightens the significance and the responsibilities of sane pediatric medicine. Without adequate medical safeguards for child hygiene, we may anticipate an increase in the influence of unscientific cults and of superficial forms of psychology counseling, mental testing, and personality guidance. The protection of the mental health of the oncoming generation should be based upon an individualized medical protection of infants and children. Developmental pediatrics is a form of clinical medicine which is especially concerned with the diagnosis and supervision of child development.

The mounting emphasis on mental health is in part due to the stress and hardship of the troubled times in which we live, and into which babies are being thrust. But the emphasis is also a natural outcome of the progress of medical knowledge.

Biologic and clinical science has demonstrated the intimate relationship of structure and function to such a degree that the old antitheses of mind versus body, heredity versus environment, and psyche versus soma have lost much of their force. The organism is regarded as an indivisible unit in which physical well-being and mental welfare are reciprocal and inseparable. This monistic outlook has such far-reaching implications for medicine, that it has recently taken on the formidable, hyphenated designation, psycho-somatics. In fact, if we drop the hyphen, the union of psyche and soma becomes complete!

Psychosomatic medicine is nothing new. It simply represents a more incisive recognition of the interaction and basic identity of physical and functional factors. Development, likewise, is a unifying concept which acknowledges that the laws and mechanisms of growth apply equally to body and mind. The infant comes by his mind (psyche) in the same embryologic way that he comes by his body (soma).

#### DEVELOPMENT AS A CLINICAL PROBLEM

But development is a living process, as well as a philosophical concept—a process as real as respiration or metabolism. The nature of this process is being investigated by a great variety of ingenious methods, both in lower and higher organisms. Growth, in all its aspects, normal and abnormal, has become the central problem of the biologic sciences. It is now apparent that the growth of tissues, organs, and behavior is obedient to universal laws of developmental morphology. These laws make for a certain degree of predictability of growth phenomena. As our knowledge of these laws deepens, human growth will come increasingly within the scope of clinical diagnosis and medical control.

All this rapidly evolving science is destined to make itself felt in the procedures of clinical pediatrics. In health and in disease the child will be more and more appraised in terms of growth characteristics and of developmental status. (We use the words *growth* and *development* interchangeably.)

#### INDICES OF DEVELOPMENT

Developmental status manifests itself in three major kinds of signs and symptoms: anatomic, physiologic, and behavioral. All of these manifestations

are important from the standpoint of a developmentally oriented pediatrics.

*Anatomic* indices become significant when they go beyond mere height and weight, and deal with girths, body proportions, somatotypes, and growth rates. The new interest in the physical anthropology of the child will probably lead to rapid photographic, and other methods of recording, which sum up valuable data pertaining to constitutional type.

*Physiologic* indicators can furnish much evidence concerning growth conditions because the bodily states of the organism change with age. With the remarkable advances now under way in biochemistry, electrometry, and micro-measurements, the physiologic diagnosis of infant development may in time reach a high degree of refinement and accuracy.

*Behavior*, however, will always remain the most comprehensive and the most sensitive indicator of developmental status. Medically considered, the infant is an action system which reveals itself in patterns of behavior. His behavior characteristics and capacities infallibly express the maturity of his neuro-motor equipment and the achieved efficiency of his total organism.

The developmental diagnosis of infant behavior, accordingly, constitutes the major task of a developmental pediatrics. Anatomic and physiologic criteria of growth and well-being can never be safely ignored or slighted; but they must always be correlated with the crucial criterion of behavior. The motor, the adaptive, the language, and the personal-social behavior of the child sums up most completely his capacity to grow.

To appraise his behavior we need systematic methods of interview, observation, and diagnosis. To elicit significant behavior patterns we must use standard techniques skilfully adapted to individual and age differences. The examination must be conducted formally, with precision of purpose. In some twenty minutes we aim to have the infant display his most characteristic responses: his postural adjustments, his oculomotor control, his visual and auditory perceptiveness, his coordination of eyes and hands, his prehension, manipulation, and exploitiveness; his social awareness and communicativeness; the range and patterns of his attention, his general adaptivity, alertness, and competence to meet the total sequence of the examination. An amazingly rich array of significant behavior patterns can be evoked by a standardized sequence which uses the plain appurtenances of a crib, a table surface, and a series of simple test-objects.

#### THE FUNCTIONS OF DEVELOPMENTAL DIAGNOSIS

In the hands of a clinician, who can bring a background of experience to bear upon his findings, a developmental examination of behavior serves at least five functions:

1. It ascertains the stages and patterns of developmental maturity in normal, subnormal, and superior infants.
2. It analyzes the total behavior equipment into components and makes possible differential diagnoses of normality, amentia, and specific developmental deviations.

3. It brings to light neurological defects and sensory impairments not disclosed by ordinary methods of clinical examination. (It is indispensable for detecting many mild and obscure forms of cerebral injury.)
4. It supplies important objective information concerning emotional traits and the organization of personality.
5. It implements a constructive type of developmental supervision. Periodic developmental examinations define the growth pattern peculiar to the individual child and become the basis of a consecutive individualized child and parent guidance.

#### MEDICAL EDUCATION FOR DEVELOPMENTAL PEDIATRICS

When the functions of developmental pediatrics are stated in the foregoing terms, it is clear that a more fundamental training of physicians in this field of medicine is indicated. This training should begin in the undergraduate years and may be carried through to a high level of postgraduate specialization. The medical student in his preclinical and clinical years should have more systematic instruction in the physical and physiologic aspects of child development. This need not entail a multiplication of independent courses. On the contrary, an adaptable educational program would correlate an increasing amount of teaching and demonstration about a few key subjects such as growth and development.

The student of pediatrics, in particular, should be infused with the doctrine of development, because this alone can give him adequate perspective for appraising the normal and abnormal symptomatology of infancy. By systematic consideration of the somatic, physiologic, and behavioral manifestations of development, it will be possible to raise the study of normality to the dignity of a clinical subject. Clinical and supervisory pediatrics is preeminently concerned with the protection and the augmentation of normal well-being. For this reason it is anomalous that the critical diagnosis and interpretation of normal child development has such meager status in medical education.

Training at a postgraduate level should be associated with internships and residencies. This will become possible only when hospitals and teaching centers recognize the field of developmental pediatrics as a subspecialty which must have distinctive facilities in the form of a separate locus, appropriate equipment, and expert personnel on a par with other diagnostic subdivisions.

A well-grounded pediatrician can be trained to expertness in one or two years of full-time participation in a diagnostic and advisory service which deals with a wide range of normal and abnormal developmental conditions. Ideally, this specialized training should include the periodic contacts of well-baby supervision, the examination of infants prior to adoption and foster home placement and of preschool children under nursery school auspices, and the differential diagnosis of a diverse array of mild and severe abnormalities, including retardation, amentias, aplasias, malformations, degenerative processes, cerebral injuries and other traumas, anoxemia, infections and toxic lesions, endocrine dysfunctions, sensorimotor handicaps, and environmental shocks and stresses.



## DEVELOPMENTAL PEDIATRICS AND PSYCHIATRY

The mere enumeration of all these conditions reminds us how gravely they may be neglected in the absence of facilities for developmental diagnosis and supervision. In virtually every instance, whether the child be normal, handicapped, or defective, the crucial medical and social problems call for a judgment as to developmental status, developmental outlook, developmental guidance. And since these problems all gravitate in their first, infant phase to the pediatrician and the family doctor, the primary responsibility for their solution gravitates to the pediatric contingent of the medical profession.

We know of no other specialty equipped to take over this inevitable task of preventive and supervisory medicine. Allergist, cardiologist, orthopedist, neurologist, and psychiatrist all have a role to play; but the pediatrician alone is conversant with the infant as a whole, and he is preeminently concerned with the maintenance of a forward moving sequence of development. The pediatrician is adept with babies, and by tradition he is interested in their total welfare. So he is in a favorable position to go along with the new trends of psychosomatic medicine, and with the new scientific emphasis on the dynamics of development.

The historical evolution of clinical pediatrics has very naturally brought about a preventive outlook upon the period of infancy and early childhood. Psychiatry, on the other hand, has derived its concepts largely from the psychopathology of the adult, and has been preoccupied with the interpretation and treatment of mental disease. Recent extensions into the adolescent and pre-adolescent period therefore reflect the methods and the outlook of adult psychiatry. Accordingly, child psychiatry has made its most characteristic contribution in psychotherapy, and in the elucidation of the abnormal behavior which manifests itself in juvenile conflicts with adult culture.

Experts in the field of abnormal child behavior will always be in strong demand to serve as consultants or as members of a diagnostic group. In view of the historical trends of psychiatric medicine, this represents a logical function of a clinical child psychiatry.

For the vast work of preventive mental hygiene, however, we must look to pediatric medicine. In principle and in actuality, pediatrics is already committed to a form of supervisory health protection which includes mental as well as physical welfare. Since bodily growth and psychic development cannot be divorced, the methods of developmental pediatrics contain the essence of a preventive psychiatry of infancy and childhood.

To understand any child, whether normal or handicapped, we must understand his ways of growth. These ways of growth are the sum and substance of his psychic constitution, or his psychosomatic constitution. Only as we become aware of these ways of growth, can we plan adequate procedures of guidance and control. Here lies the significance of a periodic examination of infant behavior as a pediatric approach to the mental hygiene of early child development.

## AREAS OF APPLICATION

A brief outline of the possible areas of application will serve to summarize the main thesis of this paper.

Developmental pediatrics is a special form of clinical procedure designed for the diagnosis and supervision of early child development.

It is equally concerned with normal and abnormal development because its aims are preventive, positive, and directive.

The scientific foundations and techniques of developmental diagnosis are now in the making. The American Board of Pediatrics has recognized the new trends by a pioneering policy which has made knowledge of growth and development a prerequisite for specialty certification.

This knowledge should embrace the behavioral as well as the somatic and physiologic aspects of child development. Behavior is the most inclusive and significant index of developmental status and is the most essential clue to the developmental needs of infant and child.

Periodic determinations of developmental status serve to protect the mental health both of normal and of handicapped children.

For reasons of social welfare, such developmental supervision is of pre-eminent importance during the first three or five years of life.

For concreteness, several areas and degrees of application of developmental pediatrics may be outlined as follows:

*General Pediatric Practice.*—The busy practitioner who has little time for extras of any kind should nevertheless consider the value of a routine behavior inventory. This inventory would be a check list of behavior items ascertained by questioning, directed observation, and a few simple tests. A minimum of eight items covering the motor, language, adaptive, and personal-social reactions of the child could be used to screen significant defects and deviations. In conjunction with the physical record such items may at times assume much importance in the later developmental history of the child.

*Dispensaries, Children's Wards, and Temporary Homes.*—A routine behavior inventory can serve a similar screening purpose where numbers are large and personnel is limited.

*Child Care Institutions and Agencies.*—Here child protection should go one step beyond physical health. More careful appraisals of developmental status should be made from time to time. Even if nurses, social workers, and psychologists assist in making the records, the responsibility of interpretive diagnosis should remain with the supervising physician. Infants and young children should not be placed in adoption without a thorough developmental examination, followed by a period of probation.

*Individualized Pediatric Supervision.*—Pediatricians with requisite skill and aptitude can incorporate varying degrees of formal developmental work into their regular nutrition and health supervision. Much can be done, much is being done, by way of developmental guidance, in a purely incidental manner. Much more could be done if this guidance were specifically related to a

series of planned examinations at key ages. Consecutive appraisals with standardized procedures would lead to more insight into the individuality of the child's growth pattern as expressed in his modes of development.

The same kind of supervision would be highly desirable in well-baby conferences. There is a growing realization that the methods of these conferences should be more thoroughgoing, which is to say that they should be more individualized and focus more fully on developmental factors.

*Medical Teaching Centers and Regional Hospitals.*—Here the need of a highly specialized form of developmental pediatrics is now unmistakable. To the large hospitals, research and teaching centers come an unending stream of infants and young children who present developmental complications of far-reaching and long-enduring import. Too often these young patients receive only a delimited categorical diagnosis which overlooks or slights the developmental essence of their condition. But it is the developmental aspect which is of supreme concern to the parents. The medical management of these cases of abnormality, impairment, and handicap, becomes more considerate with a developmental approach, which leads to constructive follow-up contacts during the trying early years when parents profit most from timely and skilful guidance. Incidentally, a careful developmental examination which parents are permitted to observe often helps them to better understand their child and the methods of care which he will need at their hands.

The first and foremost function of developmental pediatrics in a large clinical center is diagnosis; because diagnosis involves a concrete estimate of growth potentialities and thereby serves to define the details of care and management. Diagnosis becomes cumulative and progressive with follow-up contacts. In developmental supervision, interpretive diagnosis and advisory guidance are closely combined in the interest of child and parent.

The recognition and interpretation of developmental defects and deviations, however, requires a vivid acquaintance with the characteristics of normality. The clinician will, therefore, see to it that he and his students make ample contact with relatively normal infants and children at varying age levels. Provisions for the developmental supervision of "normal" infants may some day become an accepted feature of hospitals which also function as health centers. Certainly the public health activities of the future will become increasingly clinical; that is, individualized, and they will place a prior premium on mental health in infancy and preschool childhood.

In view of the great dearth of experienced developmental pediatricians, we shall have to look to medical schools and teaching centers for the training of specialists in this most generalized form of clinical medicine. The larger institutions can well set aside a special locus, with simple but hospitable arrangements designed for the conduct of systematic, formalized, developmental examinations. These arrangements would be available to normal infants under health supervision, as well as to the deviant and defective. When such provisions are deliberately planned and utilized by expert clinicians, developmental pediatrics will come into its own both routinely and as a diagnostic specialty.

## TETANUS

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DURING the years 1921 to 1946 there have been seventy patients with tetanus admitted to the wards of the Hospital for Sick Children, Toronto. It is the purpose of this report to present some observations on this disease with special reference to improvement in methods of treatment.

### CLINICAL ASPECTS

We have had an opportunity to study the value of administering antitoxin by different routes. Usually, the source of the infection in these patients could be traced to a scratch, a cut, or a punctured wound. In fifteen of the seventy patients, no history of injury was obtained. There was a great variation in the clinical course from very severe to very mild cases. Incubation periods varied from one day to one month, and usually, the shorter the period, the more seriously ill was the patient. Although the prognosis was definitely less favorable in patients with a short incubation period, the invasion period was of more importance in determining the prognosis; the more rapid the invasion period, the more likely the patient was to succumb.

It was found that most of the cases occurred during July, August, and September, and that the majority of the patients ranged in age from 3 to 13 years. Two were in the neonatal period. Fifty-three were boys and seventeen were girls.

### TREATMENT

The patients are kept in a quiet, darkened room with nurses in constant attendance. Fluids by mouth are given as long as possible if they do not cause spasms and choking. Intravenous fluids are given when oral feedings are no longer possible. Antitoxin is administered intramuscularly in doses of from 40,000 to 300,000 units in the course of the first few days after admission, the dosage depending upon the severity of the signs (i.e., degree and frequency of spasm). If a respiratory infection develops during the course of treatment, penicillin is administered. Seconal, as suggested by Dietrich,<sup>11</sup> has been used almost exclusively in doses of  $\frac{3}{4}$  to 3 grains depending on the age of the patient and the severity of the spasms. Wounds have not been excised in recent years, as some patients were worse after this procedure. The wound, however, should be cleansed by the usual conservative methods.

### RESULTS

The results are shown in Chart 1. The fatality rate from 1921 to August, 1946, was 47 per cent. This rate takes into consideration all patients with tetanus, including three patients who died before treatment could be instigated,

From the Department of Pediatrics, University of Toronto, and the Hospital for Sick Children, under the direction of Alan Brown, M.D., F.R.C.P. (London).

and one patient, the history of whom showed no record of the amount of antitoxin, although we believe antitoxin had been given. During the years 1921 to 1928, there was a patient fatality rate of 66.6 per cent, during 1929 to 1935 the rate was 55.5 per cent, and from 1936 to August, 1946, it had fallen to 28 per cent. We believe that these results over a twenty-five-year period reveal that our treatment has improved in respect of the route of administration of antitoxin. We believe that there are other factors as well which explain this result; namely, continuous nursing, more careful feeding of the patients, the use of seconal as a sedative, and the observation that many patients in recent years have had a less severe type of illness.

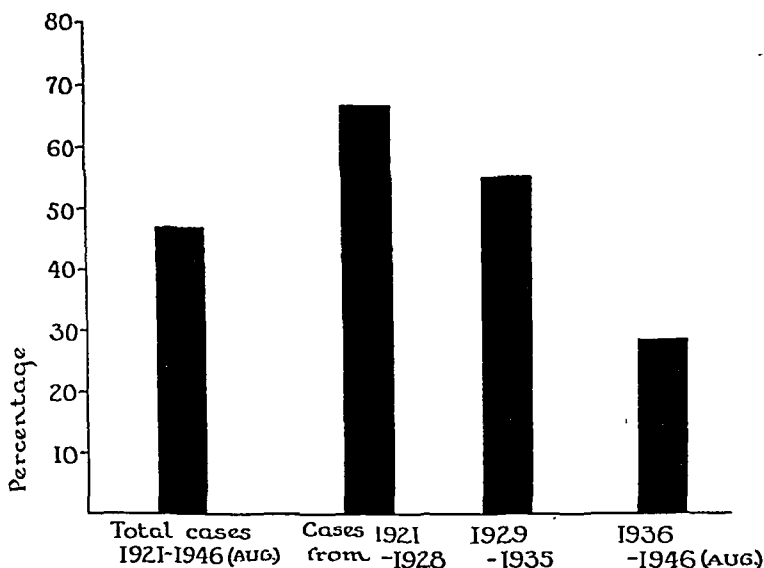


Chart 1.—Tetanus fatality rate in per cent for seventy cases from 1921 to August, 1946.

#### DISCUSSION

Due to the fact that fifteen of our seventy patients had no history of injury, that repeated doses of antitoxin sensitize children to horse serum, and that many children are allergic, we believe that consideration of the prevention of this disease in all children is paramount.

The prevention of tetanus with tetanus toxoid should be practiced in conjunction with administration of diphtheria toxoid and whooping cough vaccine.

In evaluating the treatment of our patients, we believe it is worth-while to discuss some of the more important observations. In the period from 1929 to 1935, the majority of patients received large, intravenous doses of antitoxin. A few of these patients developed reactions soon after intravenous therapy which suggested anaphylactic shock. We felt at times that this produced a pulmonary edema which could have resulted from antitoxin and fluids intravenously in the presence of heavy sedation. We believe that intrathecal administration of antitoxin is unsound and probably dangerous. This method of

administration of serum produces a sterile meningitis which adds to the patient's discomfort and may decrease his chances of recovery. In the past few years, 1940 to August, 1946, fifteen patients received tetanus antitoxin by the intramuscular route exclusively. In addition, most of them received seconal as the sedative. We believe that this method of administration of antitoxin is to be preferred to either the intravenous or intrathecal routes and should be used exclusively. In a review of these patients it will be seen in Chart II that methods of treatment formerly used, in which antitoxin was given by various routes or combinations of routes, resulted in, as many deaths as recoveries. In the group of fifteen patients to which intramuscular injections of antitoxin were given, there were only two deaths and thirteen recoveries.

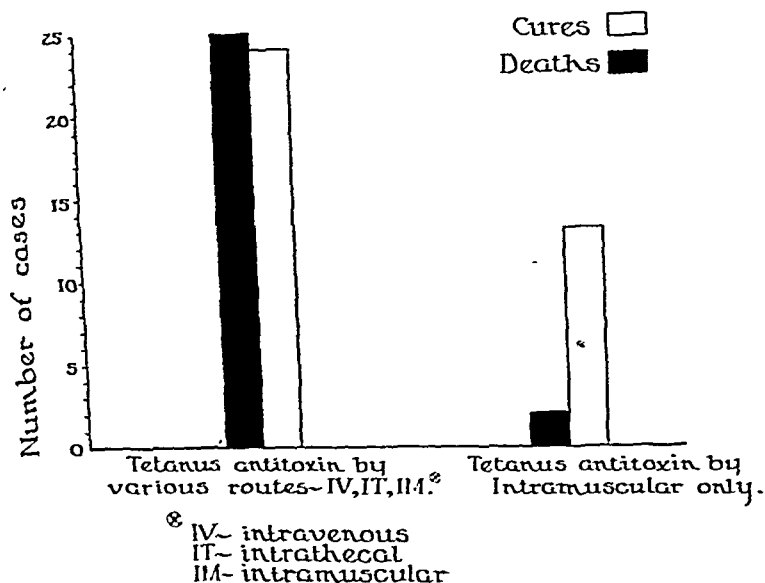


Chart 2.—Tetanus antitoxin in treatment of sixty-four patients from 1921 to August, 1946.

It may be well at this stage to discuss the measurement of the blood antitoxic unit before and following therapeutic doses of tetanus antitoxin. This was done in a few of our patients. It is known that a dose of tetanus antitoxin of therapeutic proportions elevates the blood antitoxin to levels which have been assumed to be sufficient to neutralize disseminating toxin. This is rational in theory, yet in practice we have observed patients, who received amounts of antitoxin resulting in satisfactory blood levels, improve during the days in which antitoxin was given; later, these patients developed more frequent spasms, were then given more antitoxin as well as continued sedation, and have shown definite clinical improvement. It may be argued that it was not the additional antitoxin that had the desirable effect, yet after noticing the improvement in certain patients over some years past, we believe that additional amounts of antitoxin are beneficial.

## SUMMARY

1. Seventy cases of tetanus are reported.
2. In fifteen patients there was no history of injury.
3. The incubation period, invasion period, the seasonal, age, and sex incidence of these cases are mentioned.
4. Active immunization as a means of preventing tetanus is discussed and recommended for all children.
5. In treatment, tetanus antitoxin is recommended in doses of 40,000 to 300,000 units, to be given intramuscularly.
6. We do not recommend that antitoxin be given either intravenously or intrathecally.
7. Seconal is the sedative of choice.
8. Nurses should be in constant attendance and the patient kept in a quiet, darkened room.
9. Surgical excision of the focus in the early acute stage of the disease is not recommended. The wound may be treated conservatively by the removal of easily accessible splinters or other objects, properly cleaned, and protected.
10. Results of treatment in the period from 1921 to August, 1946, show that in the seventy patients there was an overall fatality rate of 47 per cent. From 1921 to 1928 the fatality rate was 66.6 per cent, from 1929 to 1935 it was 55.5 per cent; and from 1936 to August, 1946, it was 28.5 per cent.

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## Case Reports

### REPORT ON A PREMATURE INFANT WEIGHING 820 GRAMS

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THE number of premature infants weighing less than 900 Gm. and surviving is small, so that a case of this sort is of interest. The smallest infant reported was by Fischer-Ban,<sup>1</sup> weight, 600 Gm. The smallest infant reported in this country was by Hoffman,<sup>2</sup> weight, 735 Gm. at birth. Dr. Julius H. Hess<sup>3</sup> stated, "The child mortality after cesarean section was strikingly high (45 per cent), which, however, was not due to the operation but to complications on the part of the mother, namely, eclampsia and placenta previa." In our case the infant was not only premature (twenty-seven weeks' gestation) but was delivered by section because of eclampsia and premature separation of the placenta.

The mother of this infant was a white woman, aged 33, with a history of one previous abortion. Her last period had been Jan. 24, 1943. On August 13 she came into the hospital with severe symptoms of toxemia, semicomatose, blood pressure 220/110, and vaginal bleeding. After eighteen hours of treatment with intravenous fluids, morphine, a cesarean section was performed by Dr. A. F. Lash, and a female fetus delivered. There was a large retroplacental hematoma.

The infant at birth was cyanotic, showed no muscular activity, no cry, and very feeble respiratory movements. Immediately after birth the mouth was cleared with a catheter, and the infant placed into an oxygen incubator of the Hess type which had already been made ready in the premature nursery. An ampule of Vitamin K was given and repeated every six hours for 4 doses. The weight a few hours after birth was 820 Gm., and length 30 centimeter.

Nothing was given by mouth for twelve hours, then sterile water about 5 drops every two hours for twelve hours, then breast milk diluted one-half with saline for forty-eight hours, then full strength breast milk. After eight days she was taking 4 to 6 c.c. every two hours. On the fifth day the first audible cry was heard. The incubator temperature was kept at 90° F. up to the ninth day, when the baby began to run a slight temperature; after this it was lowered to 84° F. From then on, no temperature difficulties were encountered except on the eighteenth day when the incubator was accidentally heated to 100° F. and the baby's temperature went to 103° F. No ill effects were noted.

The weight, which started at 820 Gm., was 893 Gm. on the twelfth day (no intermediate weighing was done). On the twenty-third day the infant weighed 1,015 Gm.; on the twenty-ninth day, 1,090 Gm.; on the thirty-fourth day, 1,175 Gm.; on the forty-second day, 1,309 Gm.; on the forty-fourth day, 1,300 Gm.; on the forty-sixth day, 1,390 Gm.; on the fifty-fourth day, 1,514 Gm.; on the sixty-first day, 1,816 Gm.; and on the seventy-eighth day, 2,327 grams. On leaving the hospital on the eighty-fifth day, she weighed 2,549 grams. Cyanosis and irregular respiration were present up to the fifth day, after which very little respiratory difficulty was encountered. Oxygen was continuous, however, up to the twenty-sixth day, and intermittent (after feedings) up to the forty-fourth day. Feedings were by dropper up to the twenty-fourth day, by the premature nursery bottle up to the thirty-fifth day (1,175 Gm.), then by ordinary bottle. No regurgitation was encountered except when the feedings were pushed faster, or more than the baby wanted.



Straight breast milk was given from the third to the fifty-fifth day (supplied by the Chicago Board of Health), then a gradual shift to lactic acid milk was begun. The lactic acid milk had to be given double strength to maintain weight gain. In addition, Vitamin B complex, and orange juice were started on the twenty-fourth day, oleum percomorphum on the twenty-ninth day, and iron and ammonium citrate, a 50 per cent solution, 5 drops in each bottle, on the fifth day.

Father's blood, 2 c.c., diluted with 2 c.c. of saline was given at six hours, at twenty-four hours, and then every other day for three weeks, then every five days until discharge, the amount being gradually increased.

On October 4 (forty-eighth day), the blood count was: red blood cells, 3,700,000; white blood cells, 10,200; hemoglobin 12.1 Gm.; 15 per cent segmented cells; 3 eosinophiles, 1 basophile, 71 small lymphocytes, and 10 monocytes. On October 19 (just before iron was started), the count was: red blood cells, 3,100,000; white blood cells, 10,100; hemoglobin, 11.0 Gm.; segmented cells 18%; eosinophiles 6; small lymphocytes 69; monocytes 6; and 1 Türk cell.

Further feedings consisted of cereal begun at 45 days, vegetables at 4 months, and the usual form of feeding from then on. At 3 months, the milk was changed to evaporated milk, water and dextri-maltose, and at 9 months to cow's milk.

At one year the baby weighed 15 pounds, 9 ounces, was 23 inches long, crawled, and had four teeth. Though small, she acted like a normal infant of her age. At 2 years she weighed 24 pounds, was 29 inches tall, walked and ran normally, and spoke short sentences. At 3 years she weighs 30 pounds, is 35 inches tall, walks, runs, talks well, and seems quite bright for her age. At 18 months she had bronchopneumonia, at 26 months measles, and several attacks of tonsillitis at various times. With each illness, she ran a temperature of 104° F. or over, but recovered quickly with no ill effects.

I believe part of our success in this case was due to a minimum of manipulation at birth, and careful, patient management on the nurses part in the early stages.

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## INFANTILE TOXOPLASMOSIS

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REPORTS of human toxoplasmosis have been increasingly frequent in the past few years. Among various factors which have contributed to this increased incidence are more accurate knowledge of the history and morphology of the toxoplasma organisms and their demonstration within the monocyctic phagocytes of the body, the development of neutralization antibody and complement fixation tests, the transmission of the condition to experimental animals by infected body fluids or tissues, and a better appreciation of the various clinical aspects of the disease.

The progress which has been made in diagnosis is indicated by the recognition of four fairly distinct clinical types,<sup>1,2</sup> each with characteristic signs and symptoms. These may be briefly outlined as follows: (1) the congenital or infantile type with the infection occurring either in utero or shortly after birth and giving signs of cerebral injury, such as convulsions, hydrocephalus, microcephalus, mental retardation, chorioretinitis, or calcification of the irregularly distributed granulomata which have occurred within the central nervous system, (2) an acquired disease in older children characterized by acute encephalitis, (3) an acute form in adults with pneumonia, and at times, a picture resembling typhus or spotted fever, and (4) a group in which high natural resistance to the organism has resulted in the production of neutralization antibodies<sup>3,4</sup> in the serum with an absence of any clinical signs attributable to the toxoplasmic infection. The case to be reported belongs to the first classification and an early tentative diagnosis of toxoplasmosis was made because of the presence of disseminated, calcified areas in roentgenograms of the skull.

The first published record of proved human toxoplasmosis was in 1939 by Wolf and associates,<sup>5</sup> in a child from whom the infection was experimentally transmitted to laboratory animals. These authors also included in this report four additional cases previously described by other investigators<sup>6, 17-19</sup> as due to an *Encephalitozoon*, and which Wolf and his associates now believe to be toxoplasmosis. These same authors<sup>5</sup> in 1942 reported six other individuals diagnosed clinically. Three of these six patients had been mentioned in a review in 1941 by Sabin,<sup>3</sup> who collected all of the proved and probable toxoplasmic infections to that date. This review summarized seventeen cases, including twelve of the infantile type, two of the acquired childhood, and three of the adult type. Four of the children were alive at the time of writing.

In 1940 Pinkerton and Weinman<sup>7</sup> described the first recognized infection in an adult. Other cases, most of which have been children, have been reported by Pinkerton and Henderson,<sup>10</sup> Levin and Moore,<sup>11</sup> Vail and associates,<sup>12</sup> Crothers,<sup>13</sup> Adams and associates,<sup>14</sup> Steiner and Kaump,<sup>15</sup> Tomlinson,<sup>16</sup> and Syverton and Slavin.<sup>2</sup>

Zuelzer,<sup>1</sup> in 1944, reported infantile toxoplasmosis in three children, two of them being identical twins.

In 1946, Pratt-Thomas and associates<sup>9</sup> summarized twenty-one deaths due to this disease, with necropsy reports. At the present time, so far as I have been able to ascertain, a total of thirty-eight cases have been reported.

From the Children's Hospital of Pittsburgh.

## CASE REPORT

C. K., a 4-year, 3-month-old, white female, was first seen on May 23, 1946, in the outpatient department of the Children's Hospital of Pittsburgh, where she was brought because of intermittent convulsions which had begun at the age of 2½ months. During the course of preliminary study, routine skull plates showed multiple intracranial calcifications, which were recognized in the x-ray department as possibly indicating infantile toxoplasmosis. The child was admitted to the hospital on June 11, 1946, for further study.

*History.*—With the exception of a lethargy lasting a few hours after birth, the baby was normal until 2½ months of age when she had a severe bout of diarrhea lasting a week. During this period of illness she had many convulsions of several minutes' duration. At 2½ years, she began to have a right-sided convulsive seizure resembling petit mal, which disappeared for fifteen months on treatment by the family doctor. About six months previous to admittance to the hospital the attacks recurred and were as frequent as five or six times a day, usually in the morning. Her eyes wavered from side to side, her head dropped for a few seconds, but there were no definite convulsive movements. She was drowsy following these attacks. The child had had no illness other than German measles in April, 1946, frequent colds, and an occasional attack of tonsillitis.

The mother had been comparatively well during pregnancy, her only complaint being that she had severe hemorrhoids. The pregnancy was of eight months' duration. Birth weight was 5½ pounds. The child cut her first tooth at 13 months and at the time of writing had twenty teeth. She sat up at 8 months and walked at the age of 2 years. At the present time she says words but does not form them into sentences. Both mother and father were living and well. The family had always lived around Pittsburgh except for the mother, who lived in New York City from 1931 to 1936. The mother had never had any illness except the usual contagious diseases and her pregnancies. There was one other child in the family, a boy aged 7 years, in perfect health. The mother had no other miscarriages and no other pregnancies. There was no history of familial diseases. The parents offered the information that at the time of birth of this child the mother was told that she had a positive Wassermann test. This was disproved at subsequent blood tests done in this city.

*Physical Examination.*—The patient was a white female child of 4 years, 3 months, fairly well developed, but definitely mentally retarded. Her weight was 33½ pounds, height, 38 inches. The head circumference was 46.35 cm. (normal, 49 cm.). There were no skull deformities. The other positive physical findings were a lateral nystagmus of both eyes. Ophthalmoscopic examination showed several large areas of chorioretinitis in the right eye. The left eye had one large area of chorioretinitis in the lower quadrant. There was a suggestion of a positive Bakinski test in the left foot. Other reflexes were normal.

*Laboratory Data.*—Hemoglobin was 12.5 Gm.; red blood cells, 4,240,000; white blood cells, 7,400; polymorphonuclears, 75 per cent; lymphocytes, 13 per cent; monocytes, 1 per cent; eosinophiles, 5 per cent; myelocytes, 6 per cent. Blood calcium was 9 mg. per cent; blood phosphorus, 5.4 mg. per cent; and blood phosphatase, 10.24 Bodansky units. The urine was negative except for an occasional pus cell and some mucous shreds, and the blood Kahn test was negative. Old tuberculin tests were negative 1:10,000 and 1:1,000; the sedimentation rate was 22 mm. per hour. Spinal fluid examination showed the pressure to be within normal limits; the fluid was clear; the cell count

was 1 lymphocyte; globulin was negative; the smear was negative and culture showed no growth. Spinal fluid sugar was 63 mg. per cent; chlorides, 715 mg. per cent; and proteins, 54.5 mg. per cent.

*X-Ray Report.*—There was a large number of small, calcified particles scattered throughout the brain. These probably represent calcifications accompanying infestation with toxoplasma (Fig. 1).

The chest, pelvis, long bones, and abdomen were entirely negative to x-ray examination.

*Psychometric Examination.*—The patient cooperated well. Her I.Q. was 65 with a mental age of 34 months. "The patient demonstrated an ability to learn. Therefore, another test in six months or a year would be indicated. She compensated for lack of speech by very meaningful gestures."

*Neutralization Antibody Test.*—On July 19, 1946, blood was taken from the patient and from the mother for neutralization antibody tests. It was centrifuged and packed in dry ice and sent to Dr. Isaac Ruchman at the Children's Research Foundation in Cincinnati. Dr. Ruchman reported positive neutralization tests for both the patient and the mother.

Ophthalmoscopic examinations were done on the mother, father, and other sibling, all of which were normal. X-rays were also done of the skulls of the mother, father, and other sibling. These were also negative. The brother of the patient was a 7-year-old boy, very healthy in appearance and well developed. He gave no history of any illness in the seven years of his life.

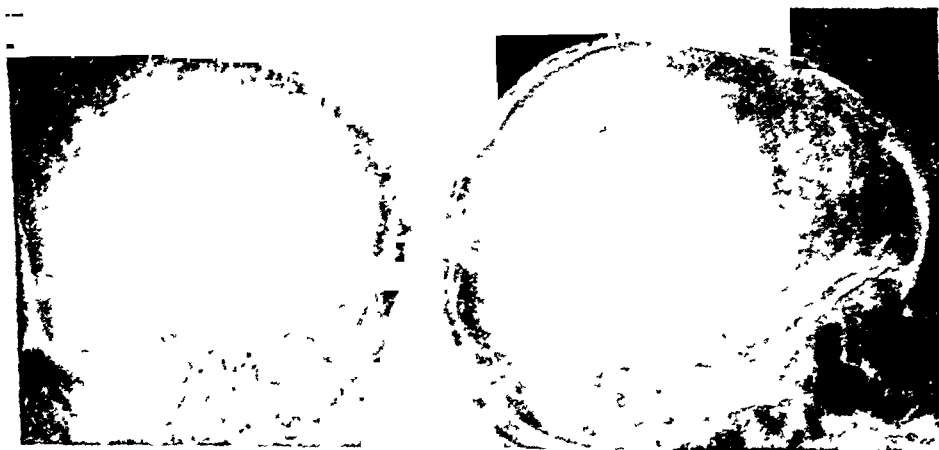


Fig. 1.—Toxoplasmic intracranial calcifications

#### DISCUSSION

This case represents a typical picture of congenital or infantile toxoplasmosis, similar to the cases reported by Wolf and associates<sup>8</sup> in 1942. The fact that the mother showed neutralization antibodies in her serum would make it seem likely that the child had acquired the disease in utero. However, it cannot definitely be proved that the diarrheal episode, which occurred at the age of 2½ months, was not the onset of the infection. The head circumference was slightly below normal, but was not definitely microcephalic. The intracerebral calcifications were extremely numerous and certainly would account for the degree of mental deficiency. Toxoplasma were not found in the spinal fluid, probably due to the long duration of the infection. Tissue biopsies were not done, and so the organism was not isolated, but certainly the clinical picture and the positive neutralization antibody tests were enough to classify

this case as one of infantile or congenital toxoplasmosis. Unfortunately, blood was not taken from the father or the other sibling, and so we do not know if either or both of them might have showed a clinically inapparent infection.

#### SUMMARY

1. A case of congenital or infantile toxoplasmosis is presented.
2. The infection was probably acquired in utero, suggested by the positive neutralization antibody tests on the mother.
3. This child represents clinically another typical case of infantile toxoplasmosis that has survived.

I wish to express my appreciation to Dr. Isaac Ruchman of the Children's Research Foundation in Cincinnati, for his work on the neutralization antibody tests on this case, and to Dr. Maud L. Menten, Pathologist, Children's Hospital of Pittsburgh, for her assistance in organizing the material presented.

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## Special Article

### THE NURSE AND THE CHILD IN GREEK LIFE

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#### SOCIAL STATUS OF THE NURSE

THE helpless condition of infancy has always called for special offices to tide the child over the first years of life. These are performed either by mother or nurse. Among the Greeks, the nurse is a familiar figure in the household, and although our knowledge of Greek domestic life must necessarily be limited from the fact that the women's apartments are so persistently closed against us, nevertheless, from sidelights furnished by our threefold source of information, the literature, the arts, and the inscriptions, we cannot help being impressed by the important place which the nurse held in the family.

In the Homeric age, mothers nursed their own children. Still, there are some instances pointing to a different practice. Odysseus, in addressing his old nurse, Eurycleia, says, "It was thou that didst nurse me here at thy own breast."<sup>1</sup> Nurses were employed as the attendants of the children, whom they amused and brought up as long as they remained in the house of the parents. Whatever function she performed, the Homeric nurse was a slave, either a captive<sup>2</sup> or purchased as an ordinary slave.<sup>3</sup> The Phrygian nurse of Hector's son may be taken as the model of the Greek nurse of an infant. We infer from her occupation that she was a slave.<sup>4</sup> Eumaeus' nurse gives us an instance of the nurse of an older child. She had been captured and sold as a slave to her master, whose hard bond she feared.<sup>5</sup> Eurycleia was higher in rank than the ordinary slave, for she had general supervision over the fifty female slaves of the household, and assisted the mistress in teaching them.<sup>6</sup> She also filled the important office of housekeeper,<sup>7</sup> was treated as a member of the family and was the friend and confidante of the mistress, who showed her great deference.<sup>8</sup> Penelope's nurse was also a trusted slave, devoted to her mistress.<sup>9</sup>

The historians have little occasion to speak of domestic life but we find mention made of a nurse in Herodotus.<sup>10</sup> This nurse is presumably a slave, for she received the commands of the parents to show the child to no one.

The nurses of tragedy were old women who had spent years in the service of their masters;<sup>11</sup> even after the child they had nursed had grown up, they were still retained in the household.<sup>12</sup> They, too, were slaves, and are spoken of as a "possession of the mistress," and "fellow slave." The fall of the mistress involved that of the nurse. Hecuba, bewailing her fate, foresaw that she who had once been the Queen of Troy, would be forced to become the nurse of children.<sup>13</sup>

It was not only captives and slaves who nursed children. In the fourth century we find at Athens free women performing the office of nurse,<sup>14</sup> and many free-born women compelled by stress of poverty to become nurses.<sup>15</sup>

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No instance is given by Plato or Aristotle of the manumission of a nurse. The nurse of new comedy was usually a slave,<sup>16</sup> still, she sometimes received her freedom "though emancipated, she yet remained in the service of her former master," her status being similar to that of the metic. We also have inscriptional evidence that women belonging to the metic classes were employed as nurses and received wages.<sup>17</sup>

Though the Athenians had a natural repugnance to the severity of the Spartan discipline, some of the Lacedemonian customs found ready acceptance in Athens. Aristophanes says that the Athenians were "Spartan-mad." For this reason, no doubt, Spartan women, whose robust health was famed throughout Greece, were often employed as nurses.<sup>18</sup> Nurses were also obtained from Corinth,<sup>19</sup> Phrygia,<sup>20</sup> and Thrace.<sup>21</sup>

Plutarch insisted that the nurse be selected with the utmost care, laying down as a fundamental qualification that she be of the Greek race.<sup>22</sup>

Such was the social status of the Greek nurse. We may conclude, then, that the nurse, though usually a slave, was sometimes manumitted, that a preference was frequently shown at Athens for the foreign-bred nurse, and that, on occasion, free women resorted to nursing as a means of gaining a livelihood.

#### DUTIES OF THE NURSE

Among the principal duties incumbent upon the nurse of an infant was the giving of the bath. We infer from several sources that it was given immediately after birth.<sup>23</sup> Some nurses preferred pure water; others, like the Spartans, bathed the child in wine, as a test of its strength, they being of the opinion that the weakly ones would faint, but the more vigorous would acquire firmness and hardness from a bath of this kind.<sup>24</sup> On a vase portraying the life of Achilles, one of the scenes shows the nurse giving the infant son of Thetis his first bath.<sup>25</sup>

Attica nurses wrapped the infant in swaddling clothes (sparguna).<sup>26</sup> As far as we can gather from the grave reliefs, these seem to have been long, narrow strips of cloth, bound like bandages around the child's body, which they completely covered from head to foot, leaving nothing but the face uncovered.<sup>27</sup> White, purple, and saffron are mentioned as colors of these bands. The practice of swaddling children is alluded to by Hesiod<sup>28</sup> and frequent reference is made to it by the tragedians.<sup>29</sup> The Theban children given over to the State were swaddled.<sup>30</sup> The nurse in the *Amphitryo* complained that Hercules was so large she could not swathe him.<sup>31</sup> How long the children were kept thus bound, we do not know, but we can hardly suppose that it was until they had reached the age of 2 years, as Plato advises.<sup>32</sup> In the third century, A.D., the child was swaddled from forty to sixty days, according to Soranus. The Spartan nurses dispensed with these swaddling bands, allowing the children to grow up unrestrained in limb and form.<sup>33</sup> Exposed children were sometimes recognized by the swaddling clothes.<sup>34</sup>

The child was suckled either by mother<sup>35</sup> or nurse.<sup>36</sup> Naturally, the practice of employing wet nurses prevailed chiefly among well-to-do mothers.

The author of *De Libris Educandis* counsels mothers to nurse their own children, and enlarge upon the advantages accruing therefrom; nevertheless, he permits the employment of wet nurses wherever the mothers cannot perform the duty themselves.<sup>37</sup> Antiphanes considered the Scythians the wisest of men because they fed their children on mare's and cow's milk, and did not entrust them to nurses, as did the Greeks.<sup>38</sup> Plato refers to definite laws regarding the nurture of children and speaks of the time when they were fed with milk.<sup>39</sup> In the community of wives and children, he would have the mothers, from a feeling of humanity, assisted in the nurture of the children by nurses, "supplying other women, having good milk."<sup>40</sup> Aristotle associates infantile maladies with the physical condition of the nurse, "children are very subject to take convulsions, and more especially those who are very well fed, most of all when they use milk that is too rich, or the milk of fleshy nurses, who are too fat. Children cut their teeth more easily if their nurses have warmer milk."<sup>41</sup> He objects to the use of wine for the young children,<sup>42</sup> and deems it unsuitable for the nurses as well. "Wines are not profitable for the nurses."<sup>43</sup> Dion Chrysostom speaks of the use of wine, nurses' milk, and bread, for children.<sup>44</sup> Hippocrates says, "I hold it is better to give children only the most diluted wine, for such will not burn up and dry the veins."<sup>45</sup> After being weaned,<sup>46</sup> children were fed on milk<sup>47</sup> and honey.<sup>48</sup> According to Athenaeus, young children thrive well on the juice of figs.<sup>49</sup> They were also fed on morsels.<sup>50</sup> The practice of first chewing the food before giving it to the child seems to have been usual, for we have several allusions to it. Democritus likens the orators to nurses "who devour the morsels themselves, and leave the saliva for the children."<sup>51</sup> Nor did it escape the ridicule of Aristophanes who says "and like children's nurses, you grudge the food you give them. You champ and champ; and for one morsel that you give the child, eat three yourself."<sup>52</sup> Athenaeus tells the absurd story of a man who had his nurse chew his food for him all his life.<sup>53</sup>

In the beautiful idyllic scene of *Illiad* 6, 389 ff., where Hector bids farewell to Andromache and his darling son, it is to the familiar arms of the nurse that the child turns, when frightened by the glancing helm. "The child shrank, crying, to the bosom of his fair girdled nurse." "And when sleep fell on him, and he ceased from his childish play, then he would slumber softly nested in his nurse's arms, having satisfied his heart with good things."

The faithful Eurycleia carries Odysseus and lays him in the arms of his grandfather that the latter might choose for him a name.<sup>54</sup> The author of the Homeric hymn to Demeter puts these words into the mouth of the goddess nurse, "Well could I nurse a young child, carrying it in my arms."<sup>55</sup> The nurse in Herodotus VI carried the child each day to the temple of Helen.<sup>56</sup> Iphigenia, speaking of Orestes, says that she left him at home, a young child, in the arms of his nurse.<sup>57</sup> At the festival of the Amphidromia, it was the nurse who carried the child around the hearth;<sup>58</sup> and in the Nurse-festival (tithenidia) at Sparta, the nurses carried the male children to the temple of Artemis.<sup>59</sup> We know that nurses walked the floor with fretful children. A good instance is given in



Menander's *Samia* where an old nurse fondles a child to her heart's content, kissing it and calling it soft names, walking around with it until it is quiet.<sup>60</sup>

In a passage of the *Laws*, where Plato lays down rules for the management of infants, he advises that infants should be kept in perpetual motion, and live as if they were always tossing at sea. He compares the principle on which religious ecstasy is cured by a strain of impassioned music, with the method of nurses, who lull their babes to sleep, not by silence but by singing, and not by holding them quiet, but by rocking them in their arms.<sup>61</sup>

This perpetual motion used by the nurse is referred to in the *Timaeus*,<sup>62</sup> and Aristotle thinks "it is of advantage to have all the movements made (of the bodies of infants) that it is possible to have made in the case of creatures so young."<sup>63</sup> Plato lays down regulations for the nurses to carry the children into the fields, to the temples, and on visits to their acquaintances until they are able to stand alone. "We are, moreover, compelling the nurses, by legal fines, to carry the children either into the fields, or to the temples, or to their acquaintances until they are sufficiently able to stand alone . . . lest their limbs become distorted while forcibly resting upon them."<sup>64</sup> This is doubtless the reason why there is no mention made of a contrivance to keep the children's limbs straight like the *Serperastra* in use among the Romans.<sup>65</sup> The Greeks were careful to develop the body of the child to have it well shaped. The writer of *De Liberis Educandis* thinks it necessary for the members of children to be shaped aright, as soon as they are born.<sup>66</sup> In the *De Virtute*, Plutarch tells us that this is the work of the nurses.<sup>67</sup> Plato, speaking of the influence of stories on the minds of children, says, that we must persuade mothers and the nurses to form the souls of their children by these stories, "even more fondly than they moulded their bodies with their hands."<sup>68</sup> This practice continued down to the days of Galen, as is shown from the following, "The nurses of infants mould their limbs as if they were of wax."<sup>69</sup>

The nurses had various contrivances into which they placed the children after they were lulled to sleep. We read that Alomena cradled her children "within a brazen shield."<sup>70</sup> Military men were accustomed to place their children in shields after birth, that they might become vigorous and strong.<sup>71</sup> A specimen of a Greek cradle, that of the infant Hermes, a little, two-handled basket, shaped like a shoe, is seen on a vase.<sup>72</sup> Another kind of cradle (*skaphe*) is mentioned as being instrumental in the recognition (*anagnorisis*) of exposed children.<sup>73</sup> Children were also exposed in a cradle (*skaphe*).<sup>74</sup> The nurse of Zeus lulled him to sleep in a golden winnowing fan.<sup>75</sup> It was considered an omen of future wealth and prosperity to place children in these winnowing fans (*likna*).<sup>76</sup> Another kind of cradle looks like a bed on rollers and answers very well to the description given by Plutarch, "such easily moving little beds as are contrived for the children."<sup>77</sup> The rocking of the cradle is mentioned by Athenaeus, "the nurse put the child in the cradle and whenever it would cry . . . would rock the cradle and lull it to sleep."<sup>78</sup>

It was natural for the nurse to amuse the children with the various kinds of toys in use in antiquity. Of these, both the literature and the art of Greece

furnish many examples. The nurse sometimes made toys for the children; for example, the wonderful ball of Zeus, "which his dear nurse Adrastea made for him."<sup>79</sup> The shaking of rattles (*krotala*) was resorted to, we learn from Pollux,<sup>80</sup> and Stobaeus.<sup>81</sup> "The rattle and timbrel with which the nurses quiet the children." A vase painting shows a nurse dangling a fruit before a child.<sup>82</sup> Plutarch speaks of dolls,<sup>83</sup> and Vitruvius mentions a Corinthian nurse who adorned the tomb of her nursling with a basket of its toys.<sup>84</sup>

To keep the child clean and to attend to all its wants were the principal occupations of the nurse.<sup>85</sup> The fondling of children and the use of pet names were resorted to by the nurses.<sup>86</sup> Demosthenes acquired the nickname "lisper" (*Batalos*) from his nurse.<sup>87</sup> In learning to walk, the children must have had many a tumble, but the nurse was always at hand to pick them up and clean them, tidy their dress, and afterward to find fault and correct them.<sup>88</sup> Epictetus speaks of a nurse beating the stone which had caused the child to stumble.<sup>89</sup> Aristotle thinks that the crying of infants should not be restrained, as it is conducive to their growth,<sup>90</sup> but Plutarch says "as the nurse says to the child. 'don't cry and you'll be taken up.'"<sup>91</sup>

By means of amulets and charms the nurses sedulously guarded the children against the pernicious influence of witchcraft and the evil eye. "I will nurse him and never I ween through any heedlessness of his nurse shall witchcraft hurt him for I know an excellent safeguard against woeful witchcraft."<sup>92</sup> The amulets were usually of a grotesque character that the sight being diverted to them should not make so strong an impression on the child.<sup>93</sup> On the approach of a stranger, the nurse in charge of a sleeping infant would spit towards him, as if to keep off from the child a possibly evil influence.<sup>94</sup> Another charm against the evil eye is referred to by St. John Chrysostom, "The women in the bath, nurses and waiting maids, take up mud and smearing it with the finger, make a mark on the child's forehead and if one ask what meaneth the clay and the mud, the answer is that it is to turn away an evil eye, witchcraft, and envy."<sup>95</sup>

At what age the children left the care of the nurses is not certain. Chrysippus allows three years to them,<sup>96</sup> and according to Plato, the boys and girls were separated at six.<sup>97</sup> It seems clear that the boys, at least, were sent early to school to keep them out of harm's way. "The very nurses will tell you as much—children should go to school because even if they are not old enough to learn, they will at least be out of mischief."<sup>98</sup>

The tie between nurses and child might continue strong through later years. She often remained with the family as the attendant, and sometimes the confidante of the young maiden. Thus, Nausicaa's old nurse lights her fire and prepares her evening meal.<sup>99</sup> The same nurse who had attended Phaedra as an infant remained in her service until the death of her mistress.<sup>100</sup> We read that the nurse accompanied the young maiden out of doors and guarded her well, looking askance at admirers who were attracted to the girl's beauty.<sup>101</sup> She was sometimes the go-between in the maiden's love affairs,<sup>102</sup> she was wont to

comfort and console her charge when grown up, and we even have an instance that a nurse was consulted in an affair of State.<sup>103</sup>

Outside of Homer, we do not find the nurse as actively engaged in duties toward the grown son, as toward the daughter, but indications of the love and gratitude evinced by young men toward the nurse of their childhood is shown in the relatively large number of monuments and epigrams dedicated to them.<sup>104</sup>

When the nurse was not occupied with the child, she owed toward the household duties which are specifically mentioned in Homer but not so clearly defined in later authors. In Homer she was the mainstay of the house, having complete charge of the domestic arrangements.<sup>105</sup> The nurse of tragedy is occupied almost exclusively with the mistress,<sup>106</sup> and in comedy she seems to have authority over some of the servants.<sup>107</sup>

Instances of the love and devotion of nurses are not wanting in the literature. From Homer down we see the nurse as a kind mother, lavishing love and affection on the child that she nursed, and willingly giving her services to one who reminded her of her master.<sup>108</sup> A picture of true devotedness is given by Herodotus, where a nurse takes an ugly child every day to the temple of Helen to implore the gift of beauty for her charge.<sup>109</sup> It was the nurse who saved Orestes from his mother after his father's murder, and she was full of love and devotedness to the child.<sup>110</sup> Examples of tender attachment are also met in real life. Demosthenes says, "She had no kind of family connection with me except that she had been my nurse."<sup>111</sup> Neglect and unkindnesses are not characteristics of the Greek nurse, as popularly conceived. Of this, we have ample evidence of the number of metaphors employed in the literature, wherein the nurse figures, always in a good sense. One's fatherland is frequently called a nurse, since the care and nurture bestowed on a man by his country is like that given a child by his nurse. We read of the "much nourishing nurse, Greece,"<sup>112</sup> "Your motherland, the most beloved nurse,"<sup>113</sup> "This thy country nursed thee,"<sup>114</sup> and many others of a similar nature.

#### EDUCATION GIVEN BY THE NURSE

The importance of the nurse in Greek life may be judged from the fact that to her as well as to the mother is entrusted the early education of the child. Quintillian says, "Those advised better who like Chrysippus think that no part of a child's life should be exempt from education, for Chrysippus, though he has allowed three years to the nurses, yet is of the opinion that the minds of children may be imbued with excellent instruction even by them."<sup>115</sup> The same author wishes nurses to be women of some knowledge. At any rate, they should be the best that circumstances allow.<sup>116</sup> Plato says the nurse taught the children to distinguish between ordinary words. "Tell me, said he, Socrates, have you a nurse, because, said he, she overlooks your cold, and does not wipe your nose, and you learn from her neither sheep nor shepherd."<sup>117</sup>

The first lessons of the nurse were imparted by stories and songs. Plato advises mothers and nurses to mould the minds of the children by means of these tales.<sup>118</sup> In ancient literature we find only isolated traces of nursery tales,

though we have sufficient evidence to prove their existence, and suggest their character.<sup>119</sup> Nurses had many ways of acting on the imagination of their young charges in order to secure their obedience, to quiet them, and put them in good humor. The choice of the tales depended upon the nurse and the intelligence of the children, who were quieted by stories after being punished.<sup>120</sup> As a substitute for the sandal, which, according to Lucian,<sup>121</sup> was energetically applied, they sometimes told the children stories of an awe-inspiring character. The time-honored bogey was always in requisition to frighten them into good behavior, while there were tales of a pleasing character for the good children.<sup>122</sup> Of the bogey, the most frequently mentioned is Lamia whose children were destroyed by the jealousy of Hera. In retaliation, she killed the children of others. She is said to devour children alive. She is portrayed as a monster, hideous and deformed, hungry for human flesh.<sup>123</sup> Belief in her is so common in Greece that if a child dies suddenly they say Lamia snatched the child.<sup>124</sup> Acco, another bugbear, carried off naughty children in a bag<sup>125</sup> and the Empusa, or hobgoblin, could assume any form she pleased.<sup>126</sup> The wolf, too, had its place in the literature.<sup>127</sup> What the children preferred to these bogeys were the stories told to put them to sleep or to amuse them. The nurses had a store of such tales; "Nurses Tales" have grown into a proverb.<sup>128</sup> Plato enlarges upon the care to be taken in the selection of these tales,<sup>129</sup> and Plutarch thinks nurses should be restrained in the choice of these stories.<sup>130</sup> Aristotol wishes to place them under the supervision of the Paedonomoi.<sup>131</sup>

On the other hand, ancient mythology is so full of humor and imagination, so rich in amusing adventure that many of these same stories might do excellent service today as nursery tales, for example: the inventiveness of Hermes, even in his cradle; the adventures of Odysseus; the labors of Hercules; the magic rings of Timolus,<sup>132</sup> the ring of Gyges, which rendered its wearer invisible;<sup>133</sup> and others of a like nature would furnish enjoyment to many a child.

There was at Athens a store of popular tales for the amusement of children. Allied to the nursery tales are the lullabies of the nurses "as old as the world and which will last as long as the world."<sup>134</sup> They seem to have been simple melodies without words, sung to a certain rhythm.<sup>135</sup> Sextus Empiricus styles them a metrical humming. To these melodies the nurses probably adapted improvised words, as we do. This view is borne out by the fact that certain specimens exist which are imitations or elaborations of those really in use at the time they were written. The lullaby of Alcumena in Theocritus is an instance.<sup>136</sup> These are but traces of a class of songs without doubt employed by the Greek mothers and nurses to lull the children to sleep.

#### MONUMENTS TO THE NURSE

The relations between nurse and master were of that sacred character which ceased not with death. Her sincere and tender affection was not only repaid during life by the master's solicitude for her well-being, but after death her memory was frequently perpetuated by the erection of monuments. The unearthing of many of these has proved a fertile source of information concerning

the nurse. Her name, sometimes her parentage, and even details of her life and virtues, find expression in the sepulchral inscription.<sup>137</sup> In addition to these, we have literary evidence of other monuments in honor of the nurse.<sup>138</sup> In keeping with the true character of the nurse is Callimachus' epigram, wherein he commemorates the goodness of the Phrygian nurse, Aeschra, to whose memory her master set up her statue, in token of gratitude for her nurture.<sup>139</sup>

Thus, from the study of the inscriptions as well as from the literature, we learn that the Greeks had for those devoted women who stood to them in place of mother a tender attachment which often continued all through life; even after the nurse's death they sought to give some expression to it by writing epitaphs and erecting monuments to her memory.

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# The Academy Study of Child Health Services

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## THE PURPOSES AND PUBLICATION OF STATE REPORTS

The facts which the Academy Study has been harvesting during 1946 are now, in 1947, ready for processing into something which should chart the future for both pediatrics as a specialty and for the child health program, the responsibility for which we share with fellow workers in child health throughout the country. The degree to which hospitals, health services, and practitioners in medicine and dentistry have supported our inquiry gives strong evidence of the esteem and trust with which the Academy is regarded. It is time we considered the probable nature of our findings and how the facts may be most effectively presented. This should be preparatory to an early definition of the policies for which the Academy stands and the development of a program for action.

In the November issue of *THE JOURNAL OF PEDIATRICS*, Dr. John P. Hubbard, the executive director of the study, described the interest which had been evidenced from many quarters in the publication of state reports and the steps which had been taken by the central office to get state chairmen and executive secretaries to share their experiences and varying points of view. It is now timely to discuss the purposes of state reports and some of the problems which will arise in the course of their publication.

The National Report of the Academy of Pediatrics will accomplish two important objectives:

1. It will provide a basis for appraising present-day pediatrics and determining how pediatricians will be trained and practice in the future. This is a matter of family interest to all members of the Academy.
2. It will provide data, supplementary to those already available, regarding facilities for the care of children, on the basis of which sounder local and national plans can be made for improving present health services. In this sense the national report can be considered a public service. It is understood that the report will not consider the question of standards. These will have to wait on future Academy action and policy decisions. First we must have the facts.

Although state reports will be narrower in scope, what they lack in breadth they should make up for in local interest. Action on a national basis may wait, but state reports should be written so as to be put to early use. They can serve the following purposes:

1. They will be of help to local medical and dental societies in showing the distribution of doctors and dentists and the contribution they are now making to child health.
2. They will provide information for the improvement of voluntary and public health programs. Too often the study is thought of as a means whereby only publicly supported health activities will be aided. Voluntary organizations such as community councils and community chests will profit equally from our work.
3. They can guide foundations and other sources of financial support in the expenditure of their funds.
4. They can provide valuable material to state groups interested in improved local services for children. There is a real need for information which will help doctors and health officials in their efforts to convince cities, towns, and counties that health work needs strengthening.

Pediatricians must consider what they wish to accomplish in terms of public service within the state and shape the state report to those ends. If objectives are less broad we shall be rightfully considered as narrow-minded and self-seeking.

The value of state reports will be proportional to the imagination and public spirit of the state chairmen and the Academy members in his state. It has been our experience

that an interest in public affairs, so much needed for the successful utilization of state findings, is more apt to be found among pediatricians in smaller towns and cities. Pediatricians in centers of population seem to feel less responsibility for children's health programs. There is a real need for men who are willing to look beyond the narrow circle of practice or hospital interests for a broader applications of their abilities. This seeming indifference to what the study can accomplish for the Academy is due to a preoccupation with clinical problems. Too many of us persist in viewing the medical scene through a microscope when a pair of binoculars would occasionally be more relevant.

There are certain misconceptions which contribute to this state of mind. Some pediatricians seem to feel that the medical needs in their state are already known. Others think that the academy has not made its motives for conducting the study sufficiently clear. There is, in some quarters, a suspicion that the Academy is being made the tool of government or even an agent of the income tax collector.

It is erroneous to assume that present information about our health services and programs is sufficient. In a state like Massachusetts its inadequacy is attested by the eagerness which various foundations and community councils have shown for facts by which to gauge their support of facilities for the care of children. In several instances they had independently gone in search of the facts. These agencies realize that voluntarily contributed dollars must be made to stretch to new limits and used only for the support of the most worthy enterprises.

It is interesting to see how meager information can be in regard to essential medical services. For example, in Massachusetts the bed capacities of a significant number of hospitals is unknown. Since they are not licensed, there is no official source for knowledge about their size, equipment, or the extent of the service they render to the public. Other obstacles to complete information are variations in the licensing laws by which institutions are under the control of various departments in the state government. Considering the diverse interests and responsibilities which governmental departments must assume, it should not be surprising that information is often so hard or impossible to obtain.

There is little collated knowledge about hospitals in terms of their capacity to give specific types of service. In instances where special control programs have been developed against pneumonia, prematurity, venereal disease, or infantile paralysis, the extent of available facilities is apt to be known, but there is no comprehensive idea as to their quality nor how well they are distributed.

Existing clinic services are pretty well known, but figures regarding the total service they give are not complete. The amount of care given to handicapped children is well defined for social security programs, but the contribution made in hospital out-patient departments is to a large extent concealed.

Practically nothing is known about the proportion of services to children rendered by practitioners, a factor which must be better estimated if any future planning is to be realistic. The dentists in the state realize that few of them treat children but, with the present interest in expanding dental health programs, it is essential that dependence be placed on more than guesswork.

Usually the number of pediatricians in a single state is not large and there are corresponding limitations to the scope of their activities. However, they can be important catalysts in any activities concerned with children. The state report is one of the means by which they can exercise this stimulation.

#### FORM OF STATE REPORTS

If state reports are to represent the Academy effectively they must be published in an attractive form and written so as to lead to well-considered action by public spirited professional and lay people. They need not be ornate, and in a rural state will necessarily be short and simple. For larger urban states with a variety of health services one should consider the possibility of two reports. The first should be a much simplified publication for general, professional, and lay consumption, which would headline the chief pediatric problems in the state, give the study findings, and make suitable recommendations for



their solution. The second could be a more lengthy report complete with tabulations for use by those with more technical interests. An average state will have to compromise between both types of report or separate the material presented so that the facts are not obscured by too many technical tables.

#### DISTRIBUTION OF STATE REPORTS

The next question to be answered is, "Who is to get the report?" The wider its distribution, the greater will be the informed public to whom we may look for intelligent support of our recommendations and any plans for their realization.

A distribution list should be drawn up and should usually include the following:

1. State medical society.
2. State dental society.
3. State board of health.
4. Foundations or other agencies contributing to the study.
5. Organizations in the state actively interested in the welfare of children.

This should include community funds and councils.

All these agencies should be asked to indicate the number of copies they will want for distribution.

#### PUBLICATION OF REPORTS

In whose name will the state report be published? What will it cost? Will copies be distributed gratis or will they be sold for a nominal sum? These are all questions for the state chairman and his associates to decide.

In states where Academy members are limited it may be wise to develop a liaison with some organization already well known for its interest in the medical problems of the community and suitable as a co-sponsor of the report. This is already being done in several of the New England states.

The ideal person to write the report would be the state chairman or the executive secretary. In some states this responsibility has been entrusted to medical men qualified in pediatrics who will be using the material as the subject for a doctoral thesis. Whoever the author may be, he must work directly under the guidance of the committee making the state study or with a special report committee.

#### STATISTICAL MATERIAL

The statistical material used as a basis for the report will come from the central office. To this will undoubtedly be added information gathered from local sources. The material from the central office will in general be of two categories. A great deal of the information will be tabulated for the State as a whole and for special county groupings. These groupings are designed to show differences between urban and rural areas, different geographic divisions and health districts. In the second category will be detailed listings of data for individual hospitals, community health services and physicians and dentists in private practice for each county and city of 10,000 or more population. It is obvious that state chairmen will wish to have adequate consulting assistance in the interpretation of this material.

#### SUMMARY

Any state report will be effective in proportion to the enthusiasm and farsightedness of the pediatricians who have produced it. Local facts enlist local support and interest. If, as many of us believe, the difficulty with certain child health programs has been their failure to recognize the peculiarities existing in individual states, the remedy should lie in better defining them so that they may receive more suitable attention in the future. Strengthening of local health services must be based in large measure on better knowledge and utilization of local health resources. The Academy has already stated that the facts disclosed by the study will be made available to interested agencies in any state. The state report is the most important medium for accomplishing this purpose.

LONDON SNEDEKER, M.D.  
Regional Consultant  
New England Area

# The Social Aspects of Medicine

## COMMUNICATIONS

I have just received the letter from Dr. Donald Paterson of the Great Ormond Street Hospital, London, whom the readers of the JOURNAL all know by reputation and whom many know personally. The letter is full of the soundest comment and advice. Dr. Paterson's letter is of particular importance because medicine in England has been through much of what is at present threatened in this country, and is at present lying like the prisoner in "The Pit and the Pendulum," with the pendulum of State Medicine swinging nearer and nearer.

I do not know how Dr. Paterson got the idea from this column "that the U. S. A. is likely to be taking steps for a State medical service." As editor of the column, I never intended that any such impression should be created. I hope personally that some way may be found to develop a program for medical care which will be so superior to a State medical service for all concerned that the thought of the latter will be abandoned. What I have tried to reiterate and reiterate in the column is the necessity for pediatricians in this country to think—to think with completely open minds—and, in the light of the facts, to develop their own plan, the most intelligent and the best plan possible to meet the new, changed demands for medical care.

E. A. P.

27 Devonshire Place,  
London, W.1.  
7th January, 1947.

Dear Dr. Park:

When I read the column allotted to you in the JOURNAL OF PEDIATRICS, I feel that the U. S. A. is likely to be taking steps for a State Medical Service rather like the steps which have been taken and passed into law in this country. Being a Canadian, I hesitate somewhat to make any comments on what has taken place, but my English paediatric friends are much too wise to commit themselves, and leave such things to people like myself.

To start with, have no doubt in your mind that a state medical service, on paper, at least, is extremely popular with the public, and is backed by both the present Government and the opposition, although they may differ about some details. One meets very few people indeed among the lay public who are not entirely enamoured of it. The trouble will be to work out a successful scheme, but unless that is done quickly it will be too late. There are very few thinking doctors who would not agree that a doctor civil servant would be much less efficient than one not in the State service. Medicine does not lend itself to bureaucratic control. If you read Wallgren's description of state medicine in Sweden in the December number of the *Canadian Medical Journal*, you will see that it is only a partial state medical service which is supplied, and the Swedish have "stood out" against full-time service. It is my experience that only a very few, very exceptional, individuals remain efficient on a full-time salary in medicine.

The terms of payment to doctors in this country have not yet been made known; for instance, we don't know whether practitioners will be paid per capita, as in the present National Health Service, or by salary, or partially in both ways. It is not possible to say what "plums" are to be offered to the profession.

In paediatrics I think every one would agree with me that the service offered the public in large cities and near university centres is excellent; it will improve over the years, but it has already attained a very high standard, and both the poor and the rich are catered for. It is in the more sparsely populated districts, where the hospital facilities are poor and the medical profession is overworked and ill-equipped, that the public suffers. In this country this was very clearly seen and realised during the war. Throughout the war period, children were evacuated from all the large cities to the surrounding country districts and

into the remote parts of Scotland and Wales. With them went the children's hospitals, the nurses, and the paediatricians. The country folk were delighted, and maintained that they had never had such medical care before. Naturally, they would like to continue this in the future. The problem is to induce the right young men and women, highly trained and ambitious, to go to these less attractive areas; there is no use offering them an increase in salary alone; they require improved hospital facilities in order to do good work; their wives and children will not be happy and satisfied unless there are educational facilities and some modicum of culture and comfort. Under a rigid state medical service, a young man could be drafted to such an area and required to stay there indefinitely, as he would in the army; we would not like to see this happen, I am sure.

Now what should one do to prepare for these inevitable changes which the public demands? I feel sure that a survey of the situation, such as I gather Colonel Hubbard is preparing for you, is certainly the first step. The magnitude of the problem is then quite clear. It seems that to attract a young man to an unattractive district, one must keep him constantly in touch with some teaching hospital; a state might well therefore be divided into regions, centered on a university. If this were kept constantly in mind, throughout the survey, it might save much labour later. In these days of modern travel, a journey of fifty or more miles on one or two days in the week to do outpatient sessions, give lectures, or make ward rounds, in a teaching hospital is not an impracticable possibility. The linking up of preventive and curative medicine in the same individual seems to us inevitable, and the school clinics and infant welfare centres should be part of the local paediatrician's duties.

I happen to be one of the people who think that there is great strength in lack of uniformity. To have a great variety of experiments in bringing about this change, and adapting methods of finance and staffing to different situations, seems to me much wiser than trying to lay down a rigid arrangement for a whole country. This tight little island with its short distances, easy communications, and dense population lends itself much better to a uniform state medical service than would the U. S. A.

Once the problem is explained to the paediatricians and they have had a survey of their own area showing what the state of affairs is at present, both as regards beds and personnel, but, much more important, showing what is required to set it right, then the medical profession must make its effort.

It seems to me inevitable that help must be sought from Federal, State or municipal authorities, particularly for capital expenditure.

If you have the hospitals right for a start, a great part of the success of your efforts is assured.

How clever the Swedish were in the constitution of their council to direct the whole affair. This is composed of doctors from the universities and not from a Ministry of Health.

When I read the article by Wallgren and noted the very small salaries received, I wondered if the doctors were realising their hopes and ambitions and were really happy.

Lord Dawson of Penn besought the profession in this country on many occasions to bring in state medical services slowly, bit by bit, as it is something which, once done, can never be undone. We earnestly hope that this tremendous experiment of "buttering" the brains and talents of the medical profession in a very thin layer over the whole of the country, rather than in a few large cities, as at present, will be a tremendous success.

Kind regards,

Sincerely yours,

(Signed) DONALD PATERSON, M.D., F.R.C.P.

December 4, 1946

Dear Dr. Park:

Elsewhere in this journal I have contributed a paper which outlines the scope and aims of developmental pediatrics.\* By developmental pediatrics we mean a form of clinical medi-

From The Clinic of Child Development, Yale University.

\*See page 183.

cine which is especially concerned with the diagnosis and supervision of child development. This phase of pediatrics has vast implications for the social aspects of medicine. I, therefore, venture this informal letter addressed to your editorial department.

We can discuss the subject without entering too deeply into the controversial issues of social legislation, but if a developmental type of pediatrics is destined to become a major feature of clinical medicine, it is not too early to consider problems of professional training. Adequate personnel is as important as adequate legislation. Fortunately, the survey of current pediatric education bids fair to become one of the most valuable features of the Academy's Study of Child Health Services. The Board of Pediatrics has been placing increasing emphasis on the field of growth and development. How can this emphasis be implemented through medical schools and hospitals? In a word, how can developmental pediatrics be brought more squarely into the scheme of pediatric education?

For the sake of discussion, I suggest that the study of child development be raised to the status of a clinical subject, with basic theoretical instruction concretely related to the clinical manifestations of normal and abnormal growth and development. This objective cannot be realized simply by adding a new subject, entitled Growth and Development, to the curriculum. Both at the undergraduate and graduate levels medical teaching needs to be correlated around fundamental themes.

For the pediatrician the fundamental center of correlation is the child as a unitary organism. To further this correlation, various fields of instruction can be focussed more definitely on the life cycle of the child, using the normal progressions of this cycle as a basic frame of reference. It is the growth cycle which gives unity to the child and which integrates the three panels of his development, the anatomic, physiologic, and behavioral. When the study of these panels is pursued too independently, instruction tends to become disjointed. To be sure, the task of correlation falls in some measure on the student, but it is a complicated task and the medical schools should assist him from the beginning to acquire an integrated outlook on the whole field of child development both in its normal and pathologic aspects. We need reorientations in medical instruction more than we need change of content. These reorientations can be accomplished by converging diversified avenues of approach upon central themes.

If development is consistently made a central theme, there are few subjects in the field of pediatrics which cannot in some way be related to factors of age and developmental maturity. A developmental approach might bring an answer to the often repeated question, Why do we teach embryology at all? The status of embryology in many schools is still somewhat undefined, if not anomalous. Embryology, however, becomes truly a basic medical science in any program of pediatric education which concentrates on the processes of child development. We must, however, adopt Huxley's point of view and give equal weight to the post-natal and prenatal aspects of human embryology. Broadly conceived, embryology includes physiologic functions as well as anatomic structures. Moreover, there is an embryology of behavior and the whole organization of the child's development can be envisaged in terms of a dynamic developmental morphology. We might also remind ourselves of Adami's wise remark that development is a process every whit as real as secretion.

The educational problem is to make this elusive process real to the student by using all possible concrete methods at our disposal. Perhaps we need an integrating textbook which will bring the anatomic, physiologic, and behavioral manifestations of growth and development into closer correlation. But even a good book can be vitalized only by contact with concrete, illustrative infants and children. The teaching task is to take the whole subject out of the academic mist and to impart a lively clinical appreciation of the stages and patterns of child development.

In our own field of developmental diagnosis, I think we have demonstrated the feasibility of concrete, intimate instruction both at undergraduate and at postgraduate levels. In addition to a basic text, we have used the following procedures: (a) self-instruction films; (b) observation (with discussion) of developmental examinations of normal infants of varying age; (c) observation and case studies of a wide diversity of developmental defects and deviations, examined on an active diagnostic service; (d) graduated participation and prac-

tice in the application of the diagnostic tests and norms. Brief comment may be made on these several methods.

The self-instruction films delineate the characteristic behavior patterns of infants at advancing ages. The student examines these films in precisely the same manner that he studies his histologic slides. By means of a personal desk viewer, under his own control, he examines the patterns of behavior, and associates them with a given level of maturity, 16 weeks or 40 weeks as the case may be. The basic films chart the normal progressions of behavior. He can study defects and deviations in the same manner. This method makes behavior as organic and as tangible as tissue. Child development is thus made a little less elusive.

But visual instruction must be supplemented by demonstration of the living, growing infant. For this purpose we arrange a series of developmental examinations of normal babies at progressive ages. The student witnesses the examinations from behind a one-way vision screen. Conferences follow immediately; they lead to comparative, systematic discussions, because the diagnostic examinations of behavior were made with a standardized technique which exposes the lawful sequences of development. Through such systematic presentation we can raise the study of normal child development to the status of a clinical subject.

The significance of normality is enhanced by similar contact with retarded, atypical, disturbed, damaged, and defective infants. Our diagnostic service provides a plentiful array of these conditions of maldevelopment. They are examined by the selfsame standardized methods employed with normal infants. Many of these infants have been repeatedly examined at earlier ages. This doubles and deepens the developmental perspective. The child, in conference, is not only compared with the normal maturity norms; he is compared with his previous self (often with previous cinema records to document the evidence). So again a comparative, normative approach serves to give reality to development as a process.

For the postgraduate physician who has already served an internship in pediatrics or neuropsychiatry, we provide a specializing externship of one or two years in duration. After an induction period of observation and of laboratory study of the self-instruction films, he is initiated into actual examinations of normal infants. As he develops skill and confidence he is given increasing responsibility with the cases admitted on the diagnostic service. He soon discovers that the behavior tests are not as simple nor as automatic as they may have appeared. He begins to respect them as diagnostic tools, which must be applied with finesse, and which become effective only as he can bring a fund of clinical experience critically to bear.

In this way he arrives at a medical outlook upon the everyday and the unusual problems of child development. The term development has now become less abstract for him. He thinks in terms of norms and patterns of maturity, of growth trends and growth capacities. He envisages the infant and child as a growing organism, whose mechanisms of development are not altogether past understanding, diagnosis, and supervisory guidance.

We know of no other way in which clinical and teaching personnel can be adequately prepared for responsibilities and leadership in the field of developmental pediatrics, a field which may well become a subspecialty recognized as such by a board of certification. Both in private practice and in public health organization there is bound to be an increasing emphasis upon a supervisory type of clinical pediatrics which will include normal as well as sick, defective, and handicapped children. To meet these mounting social demands, there will naturally be reorientations and perhaps even a mutation or two in the evolution of pediatric education.

At any rate, the current survey of the Academy invites consideration of the fundamental problem of professional training.

Sincerely,

ARNOLD GESELL

Director, The Clinic of Child Development,  
Yale University School of Medicine  
New Haven, Conn.

## Academy News and Notes

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### NOTICE

Due to the increased cost of running the *American Board of Pediatrics*, the board has found it necessary to raise the application fee to \$125.00, effective May 1, 1947.

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The following Fellows of the Academy have been released from military service:

Charles E. Abbott, Tuscaloosa, Ala. (*Army*)  
Robert D. M. Cunningham, Stamford, Conn. (*Army*)  
Francis C. McDonald, Boston, Mass. (*Navy*)  
William B. Nevius, East Orange, N. J. (*Army*)  
Charles A. Tompkins, Omaha, Neb. (*Army*)

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Dr. H. Harris Perlman, a Fellow of the Academy, has been certified by The American Board of Dermatology and Syphilology. He is the first pediatrician to be so certified.

# News and Notes

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## THE FIFTH INTERNATIONAL CONGRESS OF PEDIATRICS

The Fifth International Congress of Pediatrics will meet in New York City at the Waldorf-Astoria, July 14 to 17, 1947.

July 14 has been set aside for registration, for the first plenary session of the congress and for the viewing of the exhibits. The opening session of the congress will be held Tuesday morning, and will be followed immediately by the first of the scientific sessions of the congress which will continue through Thursday. A telephonic translation system will be installed that will do away with the loss of time of translation into the various languages and make possible the presentation and discussion of more topics.

Dr. Rustin McIntosh of New York, chairman of the Program Committee, has consulted with the various national committees in arriving at the following outline:

### I. Major Topics

1. Diseases caused by filterable viruses.
2. Chemotherapeutic agents in the control of infectious diseases.

### II. Subsidiary Topics

1. Neonatal mortality
2. Incompatibility of blood.
3. Alimentary toxicosis.
4. Bio-immunologic procedures.
5. Congenital heart disease.
6. Rheumatic fever.

### III. Sectional meetings

One session only will be given over to sectional meetings grouped under:

1. Factors in pregnancy affecting the child.
2. Future of preventive pediatrics.
3. Vitamin requirements and avitaminosis.
4. Nutrition.
5. Control of airborne infections.
6. Tuberculosis.
7. Endocrinology.
8. Insects and other vectors of infectious diseases; methods of control.

No simultaneous translation service will be available for these meetings.

The Exhibit Committee, under the cochairmanship of Dr. F. T. Mitchell, 376 S. Bellevue Blvd., Memphis 4, Tennessee, and Dr. F. F. Schwentker of Baltimore, is preparing a very extensive and comprehensive exhibit illustrating the advances in all fields of medicine, as well as in the general field of clinical pediatrics. One room will be set aside for movie demonstration. The scientific exhibit will represent the major contribution of the United States to the scientific program of the congress. Dr. Mitchell is very anxious to have all suggestions of available and suitable material sent to him at the earliest moment.

The Committee on Local Arrangements, of which Dr. Miner C. Hill of New York is chairman, has been given to understand that the hotel situation has eased up considerably and there is every prospect that it will be better next July. As soon as possible, special notices will be sent out to pediatricians regarding hotel reservations, and more details regarding program, exhibit and entertainment.

Trips to various medical centers are being planned by the committee on post congress tours in collaboration with the American Express Company, the travel agents for the congress.

The Organization Committee, composed of members from the American Academy of Pediatrics, the Pediatric Section of the American Medical Association, the American Pediatric Society, and the Society for Pediatric Research, wishes to call to the attention of each pediatrician that he can contribute greatly to the success of the undertaking by his attendance at and support of the congress. It is the hope of the committee that every American pediatrician will welcome this opportunity to act as host to the guests from foreign lands.

The sponsoring committee is as follows: Dr. Isaac A. Abt, Chicago; Dr. Amos U. Christie, Nashville; Dr. Hugh Chaplin, New York; Dr. Wilburt C. Davison, Durham; Dr. Adolph G. DeSanctis, New York; Dr. Martha M. Eliot, Washington; Dr. Lee Forrest Hill, Des Moines; Dr. Rustin McIntosh, New York; Dr. Edwards A. Park, Baltimore; Dr. Francis F. Schwenker, Baltimore; Dr. Clement A. Smith, Boston; Dr. Philip M. Stimson, New York; and Dr. Joseph Stokes, Jr., Philadelphia.

The officers are: Dr. Henry F. Helmholz, President; Dr. L. Emmett Holt, Jr., General Secretary; and Dr. Donovan J. McCune, Assistant Secretary and Treasurer.

### CITIZEN ACTION FOR CHILDREN URGED BY NATIONAL COMMISSION ON CHILDREN AND YOUTH AT FIRST CONFERENCE

Adoption of an eleven-point action program for 1947-1948 led the list of important decisions reached by the National Commission on Children and Youth at its first annual meeting held in Washington, D. C., Dec. 9 to 11, 1946.

Successor to the National Commission on Children in Wartime, this new Commission was formed in February, 1946, "to give national leadership to efforts throughout the country to provide improved opportunities for children and youth." Its members include leaders of national organizations supporting programs for children and youth, representatives of professional groups, and state and local officials working in the fields of child health, child welfare, education, recreation, and youth employment. Leonard W. Mayo, Dean, School of Applied Social Sciences, Western Reserve University, is chairman, and Edith Rockwood, United States Children's Bureau, is secretary.

Reaffirming its position that it supports no specific piece of legislation, the Commission phrased its action program in terms of basic objectives to work for through public and private channels, in the fields of social security, health, education, welfare, recreation, youth employment, state and community planning, youth participation, and international programs.

A 1950 White House Conference on children and youth received the unanimous endorsement of the members who voted that such a conference should be broadly representative and supported, so far as possible, from public funds. It was urged that both the National Commission and similar state bodies be closely identified with the planning of the White House Conference, and the programs of popular education to stimulate state and local interest in it be conducted in advance throughout the country.

Other measures adopted at this commission meeting, which was attended by sixty-two members coming from a wide range of professional and citizen groups and public agencies, twenty-four representatives of seventeen state planning commissions for children and youth, and fourteen advisers from as many Federal agencies included the following:

1. Recommendations on increasing and extending the commission's work with professional, civic, and public groups; on strengthening its relations with state planning commissions, and with public and private agencies serving children and youth in the United States Territories.
2. Commendation of the President of the United States for his directive making possible the admission into this country of unaccompanied displaced children from Europe, and requesting the United States Children's Bureau to explore appropriate ways and means for increasing the number of children to be brought to the United States.



3. Creation of subcommittees of the commission to work with various federal inter-agency committees on youth employment and education, migrant labor, health programs for school-age children, and with the President's Committee on Civil Rights.
4. Study of the reports growing out of the Attorney General's Conference for the Prevention and Control of Juvenile Delinquency.

These and other recommendations adopted by the commission grew out of three half-day discussions centering on the questions:

How can issues be resolved in order to get action?

How can support of citizens in behalf of children and youth be enlisted through state commissions for youth and national organizations?

Urging the "mobilization of all possible resources as promptly as possible" for aid to children of other nations, the commission endorsed the International Emergency Children's Fund of the United Nations. It expressed its approval of the organization of the Social Commission of the United Nation's Economic and Social Council, and its hope that the Social Commission will establish promptly a subcommission on child welfare. Commission members were urged to study and make better known the programs affecting children developed by UNESCO, the International Labour Office, the World Health Organization, and the Food and Agricultural Organization. An exchange of experts and training of personnel between the Philippine Commonwealth and the United States was recommended as well as the extension of cooperative information and training programs between the American Republics. The United States Children's Bureau and Office of Education were asked to work out child health, welfare, and education programs for children in United States-occupied Pacific areas. The commission gave its encouragement to the efforts of voluntary organizations to aid distressed children and families around the world.

Invited together for the first time since their organization, the representatives of seventeen state planning commissions and councils on children and youth participated in the commission's group discussion sessions and held two sessions of their own. The exchange of experiences which came out at these meetings showed the widespread and lively interest on the part of the states in extending services and protections for children and youth. The group recommended that their organizations be recognized as appropriate state bodies to determine the action that should be taken on the Attorney General's juvenile delinquency conference, and that the United States Children's Bureau assist such state organizations in their work by drawing up a statement of principles, standards, and methods of work.

Members of the Commission were welcomed by Watson Miller, Administrator, Federal Security Agency, and Arthur J. Altmeyer, Commissioner for Social Security of the Federal Security Agency.

#### NATIONAL COMMISSION ON CHILDREN AND YOUTH ACTION PROGRAM FOR 1947 AND 1948

To conserve the gains that have been made and to go forward toward the achievement of its purposes in behalf of all children and youth, the National Commission on Children and Youth has adopted the following action program for 1947 and 1948:

##### 1. *Extension of Social Security Programs Affecting Family Income.*—

To seek increased coverage and benefits under social insurance, public assistance programs, or by other benefits.

##### 2. *Expansion of Federal and State Cooperative Programs for Child Welfare.*—

To press for Federal and State legislation that makes possible achievement of a comprehensive program of child welfare services, within broad programs of public welfare, available in every state.

To work for better protection of the rights and welfare of children and youth through State legislation, such as laws relating to adoption, guardianship, illegitimacy, juvenile delinquency, and other aspects of child welfare.

3. *Expansion of Federal and State Cooperative Programs for Maternal and Child Health.*—

To press for Federal and State legislation that makes possible the achievement of complete health and medical care services for all mothers and children in every state, including services for crippled children.

To press for Federal and State legislation that will make possible the development of health services for school children through joint action by school and health authorities.

4. *Expansion of Mental Health and Guidance Programs for Children.*—

To work for the inclusion in health, education, and welfare programs of mental-health and guidance services for children and youth at all stages of their development.

5. *Federal and State Aid to Education.*—

To press for Federal and State financial aid to public education that will make fully available educational opportunity for all children from nursery school through high school, adapted to individual capacities and the special needs of each child.

To insure for all youth, regardless of their economic status, full access to advanced liberal, technical and professional education, in accordance with their interest and capacities.

To extend and improve all school services essential to the development of a rounded school program.

6. *Recreational Opportunity.*—

To work for the development of recreational services and facilities as a public responsibility, with Federal and State advisory services on community recreation programs.

To encourage planning for recreation by public and voluntary agencies directed toward services to all children and youth, and particularly to areas which have not yet developed such services.

7. *Improved Child Labor Legislation.*—

To press for extension of the child labor provisions of the Fair Labor Standards Act to cover all employment in or in connection with interstate commerce, including industrialized agriculture.

To raise standards of State legislation to set: a 16-year minimum age for any employment during school hours and for work at any time in manufacturing and mechanical establishments; a 14-year minimum for other employment outside of school hours; a maximum of 40 hours a week and no night work.

To extend compulsory school-attendance laws to cover all children between 6 and 18 years of age, with allowance for legal employment of those 16 and 17 years of age and exemption of high school graduates.

8. *Employment Opportunities.*—

To work for expansion of public employment facilities for counseling and placement of young people, to be developed in close relationship with schools and other community agencies.

To urge the inclusion of work opportunities for youth in public planning for full employment.

9. *State and Community Planning for Children and Youth.*—

To extend and strengthen state and community committees planning for children and youth on a continuing basis.

To obtain advisory service and assistance for such committees from the Children's Bureau and other Federal agencies.

10. *Youth Participation.*—

To encourage the cooperation of youth groups in the planning and development of community services on which they can make a contribution.

11. *International Programs.*—

To encourage, through the United Nations and other appropriate organizations, international action that will strengthen services for children and youth.

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Dr. R. E. Dyer, Director of the National Institute of Health, United States Public Health Service, Federal Security Agency, on Jan. 5, 1947, issued the following statement on the use of glycols and ultraviolet radiation in the control of air-borne infections, to answer numerous inquiries from the public:

During the past few months, several articles have appeared in the public press relative to the possible efficacy of glycol vapors and ultraviolet radiation in reducing certain infectious diseases, particularly upper respiratory diseases, such as the common cold. Due to the fact that many inquiries have been made as to the possibility of using one or both of these methods in public buildings, it is felt that a statement at this time should be made concerning the use of such installations.

Committees of the National Research Council and the American Public Health Association have studied and reviewed the data on such installations. Within the past several weeks, these two Committees separately have submitted reports. Both of these Committees feel that the use of either glycol vapors or ultraviolet radiation is still purely in the experimental stage, and that the data collected so far do not warrant the installation of such equipment in public buildings and industry in the hope of cutting down upper respiratory infection. The U. S. Public Health Service, through its research organization, the National Institute of Health, has conducted rather extensive studies on both glycol vapors and ultraviolet radiation, and fully concurs in the reports and recommendations made by the Committees of the National Research Council and the American Public Health Association. It must be emphasized that direct, unshielded ultraviolet radiation of sufficient intensity to kill microorganisms in the air is also harmful to the eyes and exposed skin of humans. These observations are not intended to indicate that the future will or will not disclose new public health values in the application of either glycols or ultraviolet radiation. Much experimentation is needed, however, before a decision can be made as to whether such application may or may not be warranted.

## Correspondence

London, England  
December, 1946

I think you may like to hear of the interest in and emphasis on child health and well-being over here, as reflected in the recent establishment of professorial chairs in child health during the past twelve months. At the end of 1945, a professorship in child health was endowed in London by the Nuffield Trust, and Dr. Alan Moncrieff was appointed to this chair.

Since then the Universities of Leeds and Sheffield have both created professorial appointments in this subject. The establishment of these new professorships in such quick succession after the close of the war stresses the importance attached to this subject in England at the present time.

A link-up between the care and study of the sick child on the one hand, and the pediatric work, chiefly preventive, of the health departments of the public local authorities on the other, is envisaged in these schemes, the intention being to coordinate all pediatric work, and to bring into harmonious relationship the activities of the hospital physicians and consultants, the family doctors, and the public health departments.

Professor Charles McNeil of Edinburgh has just retired from the Chair of Child Health, and has been succeeded by Dr. Richard Ellis, who worked some years ago for a considerable time in the Department of Pediatrics of Harvard University, under the late Dr. Kenneth Blackfan.

Discussions concerning the proposed National Health Service have been continuing throughout the year, and now the broad provisions for such a service have been entered on the statute book. It remains, however, to hammer out the details. With this in view the British Medical Association arranged a plebiscite. Every member of the medical profession was requested to fill out a voting paper stating simply whether or not he was in favor of negotiating on this matter with the Government. A negative answer is to be regarded as implying also that whoever records it will not enter a health service based on the present outlines. The result of this plebiscite has just been published, and it shows a small majority in favor of refusal to negotiate on the act as it stands at present.

Inasmuch as the provisions for a unified hospital service are, on the whole, satisfactory, roughly 50 per cent of the consultants and specialists are not averse to the act, and the fact that the control of the hospitals is planned to be under the Ministry of Health rather than local authorities, is welcomed generally. At the same time the general practitioners, still the backbone of the profession in this country, are far less pleased with the service in its present outlines as it affects them, since they see in it a threat to their professional freedom. It is apparent, therefore, that an unfortunate split of opinion has occurred among the members of the medical profession itself.

What the exact outcome will be is not possible to say at present, but it seems quite clear that National Health Service in some form will be introduced in this country, although the details have yet to be determined.

The annual meeting of the British Paediatric Association was held at Rugby again this year, and was a great success. We had the pleasure of welcoming Dr. S. W. Clausen of Rochester, N. Y., who was then visiting this country. It is always most agreeable to have pediatricians from other countries as our guests at such meetings. An abstract of the proceedings may be found in the *Archives of Disease in Childhood*, 1946.

Our diet in this country is still restricted and tends to be monotonous, but there is no doubt that it is entirely adequate, and it is not often that one sees evidence of malnutrition. We hope that the food situation will soon improve, but no critical pediatrician expects to find any falling off in the nutrition of children, whose condition during the war remained so remarkably good. In this connection it is interesting to note that Magee, in his Milroy Lectures in 1946, makes the following statements, which are undoubtedly correct:

"The public health, so far from deteriorating (*during the war*), was maintained and in many respects improved. The rates of infantile, neonatal, and maternal mortality and the still-birth rate reached the lowest levels ever. The incidence of anaemia declined, the growth rate and the condition of the teeth of school children were improved, and the general state of nutrition of the population as a whole was up to or above pre-war standards."

We are very interested in the projected International Pediatric Congress to be held in the United States in July, 1947. All of us would like to come, but on account of transport difficulties your correspondent feels that few British paediatricians will, unfortunately, find themselves able to attend.

KENNETH TALLERMAN.

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## Original Communications

### EFFECTS OF MATERNAL UNDERNUTRITION UPON THE NEWBORN INFANT IN HOLLAND (1944-1945)

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THERE has been a recent awakening of interest in nutrition during pregnancy as it may affect the fetus, and thus, the newborn infant.<sup>1-4</sup> Most publications have given highly suggestive evidence of a definite relationship, stressing the obvious importance to the field of preventive medicine. Critical analysis, however, indicates that certain links in the chain of evidence are not as strong as they ought to be. The great difficulty is to construct experimental situations producing incontrovertible proof that undesirable results of human pregnancy, either maternal or fetal, are direct consequences of maternal dietary factors. The substance of this difficulty is stated by the proposition that women who eat poor diets may well be suboptimal individuals in various other ways, as in heredity, environment, and past history of disease.<sup>5</sup> Thus, when the statement is made that "If the diet of the mother during pregnancy is poor to very poor, she will undoubtedly have an infant whose physical condition will be poor,"<sup>6</sup> we still need proof that the infant's condition is the result of the mother's diet, soundly based as the quotation would otherwise seem to be. Or, if maternal malnutrition cannot be shown to be the sole cause of the fetal subnormality, we should like to know the relative degree of its influence.

There are at least four ways of securing data which may help to clarify these relationships. The simplest, though obviously suitable for animal investigation only, is the calculated restriction of maternal intake during pregnancy. Warkany's use of this method has been brilliantly successful in demonstrating an undoubted causal relationship between inadequate diet and fetal malformations. But so extremely limited is the diet required in such experiments,<sup>7,8</sup> that the maternal animal must be fed and treated with the utmost care, lest she fail to produce any offspring whatever. A second method is that of accurate

Presented at the meeting of the Society for Pediatric Research, Skytop, Pa., May 2, 1946. The studies being reported, as well as the author's trip to Holland, were a part of a continuing research project, financed by the Nutrition Foundation, New York City, and conducted by the Department of the Maternal and Child Health, Harvard School of Public Health, and the Boston Lying in Hospital, in collaboration with the Department of Obstetrics, Harvard Medical School.

From the Departments of Pediatrics and of Obstetrics, Harvard Medical School, and the Department of Maternal and Child Health, Harvard School of Public Health, Boston.

analyses of diets voluntarily consumed by pregnant women, with later comparison of the maternal nutritional status with the outcome of pregnancy. This demands highly painstaking work, a consistently objective attitude, and a great deal of time, because so many pregnancies result satisfactorily that a large number must be studied before a statistically significant group of complications or catastrophes emerges. In the hands of several workers, notably Burke and her colleagues,<sup>1, 6, 9-11</sup> the results of such studies have been highly suggestive. A definite drawback is, again, that a group of other conditions unfavorable to the pregnancy or the fetus may be present along with improper food habits.

A third procedure, the reverse of the first, employs the directed dietary improvement of an experimental group of women, whose pregnancies are then contrasted with those of a control group not so manipulated. This, if large enough numbers are employed, complete objectivity maintained, and *the two groups exactly comparable in all aspects except the nutritional*, would perhaps be the most informative procedure. For reasons to emerge below, the ideal program for such a procedure would select the two groups at the very onset of pregnancy, if not before. The papers of Ebbs and Tisdall,<sup>12, 13</sup> the report of the People's Health League,<sup>14</sup> and that of Balfour<sup>15</sup> in England, were based on this general plan. Again, the results indicated that supplementing maternal diet with vitamin concentrates, minerals, and proteins in various combinations was followed by decline in the frequency of miscarriages, premature births, stillbirths, neonatal deaths, and toxemia of pregnancy.

A fourth plan is that of observing the effects of widespread nutritional inadequacy due to war or other calamity affecting an entire populace. This type of study takes advantage of a period of starvation as an unhappy but nevertheless potentially serviceable human experiment somewhat like those conducted with animals in the first type listed above. Statistics from the pre- and post-starvation periods furnish the only possible controls. The observations to be reported in the present communication were made upon this basis. The investigation concerned the infants born to women in Rotterdam and The Hague before, during, and after the hunger period, which began in the autumn of 1944 and terminated with the liberation of the northwestern Netherlands in May of 1945.

It was realized that while such a study offered the quick accumulation of a large amount of material, it sacrificed the accuracy of individual and dietary histories as obtained under the second method listed above. This seemed allowable if the nutritional stringency could be shown to have been sufficiently general to involve practically all women in the clinics studied. It was also clear that the results of maternal undernutrition would be measurable only insofar as they affected the infant up to the time of birth. Evaluation of infant mortality in relation to maternal diet could not be estimated under the abnormal environmental conditions into which infants were born during the critical period.

The cities of Rotterdam and The Hague were selected as having suffered as badly as any others, and offering two active maternity clinics with presumable reliable records. Amsterdam, the other great city of northwestern Holland, was not directly investigated because the same problem was under attack there by

Dr. G. K. Levy of that city. The study was begun Dec. 15, 1945, after a stop in England en route to discuss with Dr. Hugh Sinclair of the Oxford Nutrition Survey, the food situation which had obtained in Holland. Dr. Sinclair and Dr. F. J. Stare of Harvard University had both been in Western Holland immediately after the Liberation for purposes of evaluating the nutrition status before that event.<sup>16, 17</sup> Both of them gave indispensable assistance.

#### THE NUTRITIONAL BACKGROUND

The entire value of the project depended upon knowledge that the area studied had suffered such severe malnutrition as to involve the majority of pregnant women. Investigation indicated that this was the case. The specific reason for nutritional stringency in northwestern Holland was the general transportation strike against the Nazis which began Sept. 17, 1944, at the request of the Dutch Government in London, and at a time when it seemed that this part of Holland would shortly be liberated. This expectation was not fulfilled, but the strike held for the entire period until liberation in May, 1945. During this period, aptly called the hunger winter, little or no food was transported into the major cities. Other necessities of life such as fuel were also not moved, so that heat, gas, and electricity were decreasingly available. The Germans saw the resulting hardships to the Dutch as weapons which might persuade them to drop the strike, and therefore guarded the roads and canals approaching cities so that little could be smuggled in. Under the circumstances, it was possible for country dwellers to live without much distress while urban populations only a few miles away were literally starving.

Data indicating the nutritional situation as accurately as it could be recorded are shown in Fig. 1 and Tables I to III. The official distribution of food for various age groups of the populace is shown in Fig. 1, prepared by the Royal Bureau for Food Distribution in War Time. This indicates the progressive decline of food supplies in the autumn of 1944, the rough plateau reached from January to April, then a slight increase, particularly devoted to the rationing for infants, and the sharp elevation coincident with the liberation in May.

A rough idea of the resulting effect upon general health may be inferred from figures giving the deaths for all ages and sexes attributable directly to undernutrition as shown in Table I. These figures were obtained from the Municipal Bureaus of Statistics in the cities indicated.

TABLE I. DEATHS FROM UNDERNUTRITION, AT ALL AGES\*

MONTH	THE HAGUE ± 500,000†	ROTTERDAM ± 650,000	AMSTERDAM ± 700,000
January, 1945	173	125	Nov. 1, 1944 to July 1, 1945, 2,351
February	552	548	
March	644	837	
April	442	843	
May	244	244	
June	90	—	
Weekly to May	104	136	

\*From municipal records.

†Population.



The official figures upon food distribution for pregnant women (kindly furnished by Dr. Dols and Dr. van Arcken of the Directory of Food Distribution, Ministry of Agriculture) are given in Table II for representative periods from December, 1943, to December, 1945. These are averages calculated for the entire famine-stricken area. According to these figures, a low point of about 1,145 calories and 34 Gm. of protein per day for expectant mothers was reached during January of 1945, with a slight rise by April. Investigation has revealed a great deal of variation in the availability of extra rations for pregnant women; at times the status was better than that indicated, at other times (particularly as hunger progressed) it became worse. It is also abundantly clear that most adults receiving extra rations shared them with their families.

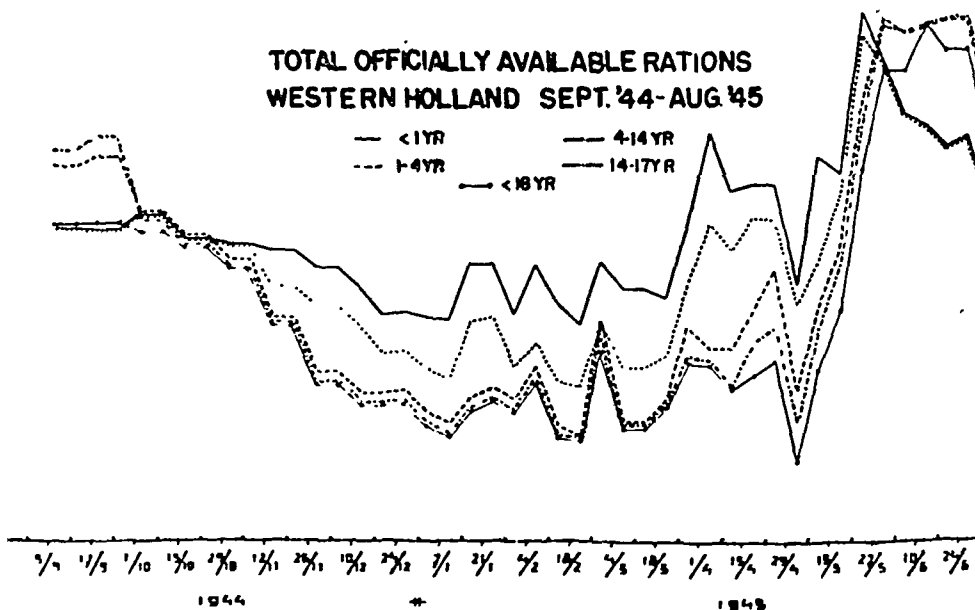


Fig. 1.—Rations available in calories per day. The decline began in October, 1944, the low point was reached in early January, 1945, and the situation remained generally bad until the sharp rise on May 15, 1945.

As the lines show, the most food was distributed to the youngest infants, the least to adults. Distribution to pregnant women is shown in Table II.

An attempt made by Dr. Sinclair to evaluate as precisely as possible the nutritional elements actually available to pregnant women in the cities of The Hague and Leiden,<sup>16</sup> is shown in Table III. Since this was prepared on the ground very soon after the Liberation, since numerous local authorities were consulted, and because of Dr. Sinclair's position as leader of a team of official investigators, it may be taken as representing as close an approximation as may be obtained. There was general agreement that the status in Rotterdam closely paralleled that of these cities.

TABLE II. OFFICIAL RATIONING TO PREGNANT WOMEN, WESTERN HOLLAND

PERIOD	CALORIES PER DAY	PROTEIN (GM.)	CARBOHYDRATE (GM.)	FAT (GM.)
December, 1943	2,353	67	481	54
July, 1944	2,109	63	342	48
October, 1944	2,099	62	331	51
January, 1945	1,144	34	177	29
April, 1945	1,427	35	215	42
July, 1945	2,546	78	344	91
October, 1945	2,808	87	428	76
December, 1945	3,042	94	456	85

TABLE III. NUTRITION AVAILABLE FOR PREGNANT WOMEN (THE HAGUE AND LEIDEN)\*

ITEM	RECOMMENDED DAILY ALLOWANCES†	SEPTEMBER, 1944	FEBRUARY, 1945	APRIL, 1945
Calories	2,500	1,925	731	912
Grams protein (vegetable)	} 85	38	24	28
(animal)		23	9	11
Grams fat		50	11	14
Milligram calcium	1,500	1,075	649	517
Milligram iron	15	16.3	9.6	10.7
I.U. vitamin A	6,000‡	1,260	445	766
Milligram thiamin	1.8	1.1	1	0.6
Milligram niacin	18	9.2	3.0	4.1
Milligram riboflavin	2.5	1.2	0.5	0.5
Milligram ascorbic acid	100	59	34	53

\*From evaluation by H. M. Sinclair, Oxford Nutrition Survey, for Supreme Headquarters Allied Expeditionary Force.

†Food and Nutrition Board, 1945.

‡Two-thirds carotene, one-third vitamin A.

One may sum up all these data in the following observations:

1. The background was one of generalized undernutrition rather than selective malnutrition. Intakes of total energy, that is, calories from all sources, were about as depressed as were individual elements. With the exception of ascorbic acid and, perhaps, thiamin (see Table III) all items of nutrition were reduced in a roughly parallel fashion, no single one being individually much lower than others.

2. The period of severe undernutrition was of brief duration. A full-term pregnancy terminating upon the last day before relief arrived would have begun under relatively good nutrition circumstances; a pregnancy in which embryonic organogenesis occurred under starvation condition in March and April would have terminated after several months of greatly improved maternal diet in November or December.

3. The populace involved had been fairly well fed up to the time of rapid deterioration in food supply.

4. The large cities were much worse off than nearby rural areas.

5. Although intelligent and painstaking attempts were made to support pregnant women by extra rations, that class was still supplied with far less calories, protein, calcium, vitamin A, niacin, and riboflavin than the allowances recommended by the Food and Nutrition Board of the National Research Council (Table III). For iron and thiamin, the deficits were less marked.

6. Relief was general, comparatively sufficient, and very abrupt.

The foregoing statements indicate that in certain important ways, the unfortunate subjects of this "nutritional experiment" in Holland were very different from those recently studied in American and English cities.<sup>2, 5, 6, 12, 14, 15, 18, 19</sup> In the latter type of material, the subjects are usually women who have eaten bad diets more or less all their adult lives, and in whose diets a few elements are particularly defective while the total caloric intake is more or less sufficient.

Testimony to the singularly abrupt, severe, and widespread character of the Dutch nutritional shortage is furnished by the prevalence of amenorrhea during the hunger months. This occurred in about 50 per cent of the female inhabitants of the cities studied, and disappeared promptly after the return of food. Reasons for believing that its cause lay in general caloric (and, perhaps especially protein) underfeeding will be presented in another publication.<sup>20</sup> The conception rate fell sufficiently to reduce the births at nine months later to about one-third of the usual figure (Table IV). Shortly after the first of March, 1946, the birth rate rose to unprecedented proportions, a fact correlated with the return of food in May, 1945.

TABLE IV. BIRTHS, CITY OF ROTTERDAM, TO SHOW DECLINE IN CONCEPTIONS DURING HUNGER\*

YEAR	AVERAGE NUMBER BIRTHS PER WEEK IN					
	JANUARY	FEBRUARY	MARCH	APRIL	MAY	JUNE
1939	<i>Weekly average, 206</i>					
1944	228	214	234	231	227	227
1945	228	262	241	270	230†	199‡
	JULY	AUGUST	SEPT.	OCT.	NOV.	DEC.
1939	<i>Weekly average, 206</i>					
1944	228	227	245	238	218	210
1945	191§	157	112¶	84**	87**	89**

\*Figures from graph furnished by Municipal Bureau of Statistics.

†Conceived in August, 1944.

‡Conceived in September, 1944

§Conceived in October, 1944

||Conceived in November, 1944.

¶Conceived in December, 1944.

\*\*Conceived in Jan., Feb., March, 1945. Food at low level.

} Food supply deteriorating.

#### MATERNAL NUTRITION AND NEWBORN INFANT SIZE

The size of the infant at birth was mainly studied by a review of records from the Midwifery (Vroedvrouen) School in Rotterdam.\* As controls, figures were first obtained from 560 births at that institution in the prewar winter of 1938-1939, and 589 in the winter of 1943-1944. This second control period was included to represent the conditions of a wartime winter preceding the one of nutritional stringency. The percentile distribution of birth weights in these two control periods was practically identical, and was in fact very similar to that for Boston infants. It therefore appeared that any deviation from expected birth weights during the hunger-winter of 1944-1945 could be ascribed to nutritional factors. It was also determined that no significant change had occurred in maternal age or parity between these control periods and the hunger period.<sup>20</sup>

\*Records from the Obstetrical Department of the Zeldwal Hospital at The Hague were also studied. These were a numerically smaller group but displayed the same tendency. They will be presented in another communication.<sup>20</sup>



theless the generally parallel course of lines connecting these two groups of percentiles in Fig. 2 indicates that change in weight was not simply a result of shortened sojourn in utero.

Study of the diagram indicates that at the beginning of the hunger-winter (period from October 1 to November 15) the percentiles were practically the same as those of Rotterdam babies in prewar times. Then began a progressive decline in weight. At the fiftieth percentile (median), which is the line of greatest statistical significance, this was steepest in the next two periods, or during the first three months of undernutrition. From February 14 to liberation at May 15, these fifty percentile lines decline very little. The fact that birth weight did not continue to fall at the same rate throughout the entire hunger period may indicate that an irreducible low point had been reached by the middle of February. More probably it testifies to the fact that maternal nutrition affects the weight of the fetus during the last half or last trimester of pregnancy only. In other words, the average fetus which lives for a full nine months in a malnourished uterus may be little or no smaller at birth than one which spends only the last three to four and one-half months under such conditions. Indeed the effect of maternal caloric intake upon fetal weight would appear to be slight at any time earlier than the sixth month of gestation.

The fact of change in birth weight is perhaps of more interest than its amount. The net change was about 240 Gm. (8 oz.) at the median. At all percentiles the amount of decline represented between 8 and 9 per cent of the weight in normal times, the percentage being only slightly greater in the heavier infants represented by the ninetieth percentile than in the light ones of the tenth percentile. Stated otherwise, both big and small infants showed a decreased birth weight of almost the same degree in proportion to the expected birth weight for normal times. It should be stated that this entire phenomenon of birth weight decline, though of statistical significance, was apparent only when infants were analyzed by groups. Many instances were encountered of mothers losing weight in late pregnancy and yet producing infants of 3.5 kg. or more. The observer who is not persuaded of any relation between maternal nutrition and fetal weight may easily find individual cases substantiating his belief.

The return of food was reflected more promptly by babies at the upper end of the weight scale than at the lower (Fig. 2). In general, the greatest degree of change again occurred in the first three months, or between May 16 and August 15. Even though the food situation for pregnant women in November and December, 1945, was supposedly not better than that of 1939, it is noteworthy that infants born in the last months of 1945 were about 200 Gm. heavier, at the mean, than were those of prewar times. The question arises as to whether the maternal body had become in some way a more efficient provider of food (or the fetus a more efficient parasite) through the experience of undernutrition before and during early pregnancy.

Measurements of birth length had been made by hospital nurses unaware that they would later be utilized for statistical analysis. There is reason to believe the methods were not conducive to great accuracy and therefore the

results are open to some question. They are shown in Fig. 3, which indicates the percentage of infants in four ranges of stature. At the top of each column, where the total number of infants in the group is recorded, it will be noted that the numbers are decidedly smaller in the later post-hunger periods. This reflection of the decline in conception during hunger makes statistical comparison from one period to the next rather uncertain. There is a statistically significant increase in percentage of short babies born in the hunger months as

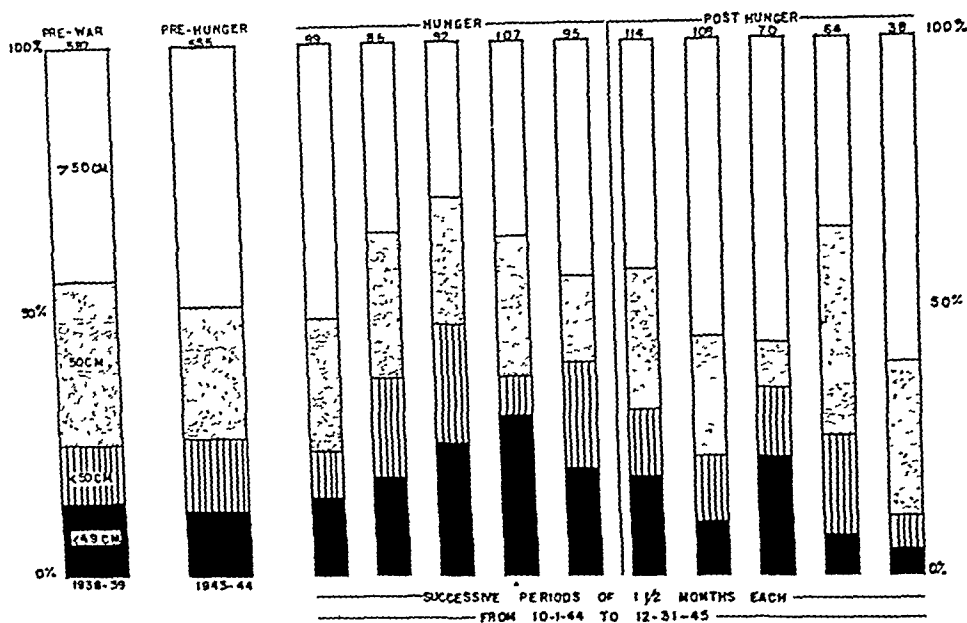


Fig. 3.—Birth length: in first column, during a prewar year; in second, during the winter previous to that of hunger; then by successive periods of six weeks each, the first five of which were during the hunger-winter, the last five, after it.

Clear part at top, per cent of infants longer than 50 cm.

Stippled areas, per cent of infants of 50 cm.

Solid black at bottom, per cent of infants less than 49 cm.

Number of infants in group shown at top of each column.

compared with those of pre- or post-hunger times, but a smooth change from period to period as maternal undernutrition developed (or was relieved) does not occur. There are evidences of a progressive trend toward short babies, especially in the first four and one-half months after hunger began, but the resulting levels are not maintained. One may say only that in terms of the data obtainable, a significant effect of maternal nutrition upon fetal length did occur. That this is not so definite as the weight change is explainable by factors mentioned above plus the principle that weight gain is a three dimensional process, while gain in length is a single dimension only.

#### OUTCOME OF PREGNANCY

Statistics upon miscarriage and, particularly, abortion, are notoriously untrustworthy during normal times. Those from the Midwifery School in Rotterdam are included in Table V, but with no attempt at drawing conclusions from

them. They show, for whatever reason, an actual decrease in births of pre-viable fetuses during the hunger period. This was followed by an increase after the Liberation. Numerous nonnutritional factors suggest themselves, among them the subsequently increasing birth rate which would cause the percentage of early termination of pregnancy to bulk large. The statistics were thus of no aid in establishing the relationship (if any) between maternal nutrition and spontaneous abortion. One can, however, record that an apparent increase in this unfavorable outcome of pregnancy did not appear during the time of under-nutrition but did appear in women conceiving at or soon after that period.

TABLE V. INCIDENCE OF UNFAVORABLE TERMINATIONS OF PREGNANCY IN ROTTERDAM

CONDITION	PREWAR, (1938-1939) 674 BIRTHS	PREHUNGER (1943-1944) 659 BIRTHS	HUNGER (1944-1945) 412 BIRTHS	POSTHUNGER (Late 1945) 464 BIRTHS
	<i>Per cent</i>			
Abortion and miscarriage	1.67	5.6	2.2	3.7
Prematurity (under 2,250 Gm.)	5.27	4.98	6.3	5.15
Stillbirth	3.5	3.2	1.8	2.5
Neonatal death (in hospital, first 10 days)	1.55	3.0	2.36	3.0
Malformation*	1.36	1.6	0.5	1.35

\*Malformation in 135 conceptions between Jan. 1 and April 1, 1945 (most severe under-nutrition) 2.42%.

The subject of prematurity raises the difficult question of how it is to be identified. Recorded maternal statements too often showed impossible discrepancies in both directions between the supposed period of gestation and the weight of the infant. This was due in part to the amenorrhea and menstrual irregularities elsewhere described. It was obviously impossible to base the diagnosis of prematurity upon this sort of information. Use of body weight and length as determining factors becomes dubious when the weights and lengths of infants are depressed by the same agent whose effect upon premature delivery is under study. For lack of anything better, it was decided to consider as premature any infant weighing 5 pound (2,250 Gm.) or less. This is a sufficiently extreme criterion so that the number of infants in this weight range would certainly not be greatly increased by the effect of fetal malnutrition during full-term pregnancy.

On this basis, as shown in Table V, premature birth was slightly more common during the hunger period than during the previous winter or in the prewar figures. Comparing 659 "pre-hunger" with 412 "hunger" pregnancies, a statistically dubious increase from 4.98 to 6.3 per cent was observed. The figure for the post-hunger months of 1945 may be somewhat elevated because of the rapid rise in the birth rate which began in January and February, 1946. The premature fore-runners of that period made up an unduly large percentage among the extraordinarily few full-term births occurring in December. Indeed, it is also possible that in a reverse manner, the declining birth rate of June and July, 1945 (Table IV) tended to reduce the percentage of small premature infants born toward the end of the hunger period in April and early May. This phenomenon deserves attention as an illustration of the way in which errors

may creep into an apparently simple statistical analysis. In any case, the maternal dietary reduction which occurred in Rotterdam was not associated with any striking tendency to premature delivery. As prematurity was not an officially reportable condition, this could not be verified for the city as a whole. However, inquiry in other hospitals in The Hague and Amsterdam did not contradict the impression gained from these figures.

Inspection of Table V shows the surprising fact that the percentage of infants born dead after the fifth month of gestation (stillbirth) was reduced during the hunger months. This observation was subjected to verification by the official mortality statistics furnished by municipal authorities in Rotterdam and other representative cities and by the National Bureau at The Hague, and was definitely substantiated. Since stillbirth tends to be reported with some accuracy (as compared with the unsatisfactory information concerning abortion), the data are presumably reliable.

Neonatal death also showed no increase in frequency during the hunger period. These hospital data are much less satisfactory than those for stillbirth in that they cannot be substantiated by comparison with official municipal or national statistics. The latter do show a high level of neonatal deaths during the hunger period, but all sources also indicate that every environmental circumstance militated against the survival of infants born at home during the months of undernutrition. Hence, except for infants born in hospitals, it is impossible to regard survival through the neonatal period as any reliable test of infant vitality during the hunger-winter.

#### CONGENITAL MALFORMATIONS

Warkany and his colleagues reason from experimental animals that the period during which maternal malnutrition might result in fetal maldevelopment is probably over by the first six or eight weeks after conception in the human.<sup>8</sup> Moreover, it appears likely by the same inference that improvement in human nutrition within four weeks after conception would probably allow the fetal organogenesis to proceed normally. This therefore necessitated investigation of infants conceived after hunger had become severe (about January 1, 1945) but not later than four to six weeks before liberation, or the first of April. The critical births were thus those occurring at term during October, November, and December, 1945. As Table IV indicates, this period offered very little material for study. There appears, as shown in the bottom line of Table V, to have been a slight increase in malformations in these post-hunger births, but in view of the numerical discrepancy between the groups contrasted and the small percentages dealt with, it is not statistically significant. Indeed it has been calculated that had it been possible to examine every baby conceived during the worst nutrition period in the two cities of Rotterdam and The Hague, the number of cases accumulated would have been insufficient to prove anything, because of the low range in which these percentages lie.

Personal examination of infants was, in fact, attempted before this statistical dilemma became apparent. A great deal of time was spent in examining every infant of appropriate age brought to the so-called Consultatie Bureaux,



or Baby Clinics, of those urban areas where local authorities considered maternal undernutrition to have been most severe. While the infants were being examined, Miss D. Ten Haaf, a trained Dutch dietitian, took nutrition histories from the mothers in sufficient detail so that they might be graded with regard to consumption of vitamin A and riboflavin, the two elements of critical importance to proper fetal development in animals. Notwithstanding the extraordinary industry and assistance rendered by the clinic nurses (who are collectively thanked) only 224 infants of proper age could be furnished, again because of the temporarily low birth rate. Frank malformations were encountered in only seven infants, or 3.1 per cent, but these seven were not concentrated among the offspring of those women whose diets had been lowest in the vitamins mentioned above.

#### LACTATION

The impressions of Dutch pediatricians and obstetricians regarding the effect of maternal undernutrition upon lactation were somewhat inconclusive. Most felt that slightly less milk had been secreted by the average mother, but that the duration of breast feeding was not greatly affected. It was impossible to secure mathematical data upon the former point in the limited amount of time available for making these investigations. Moreover, numerous non-nutritional conditions inimical to the weight gain of infants, as well as the irregular use of occasionally available substitutes all tended to make infant weight gain an uncertain measure of quantitative lactation. Therefore, clinic records were studied to determine simply the duration over which the lactation process was maintained.

The results are shown graphically in Fig. IV. Here it will be observed that in fair and poor socioeconomic surroundings about the same percentage of mothers were nursing infants of three and six months during the early and late hunger periods as before and after. A very poor district of The Hague, where nutritional conditions were extreme and deaths from starvation common, furnished the last two lines of Fig. IV. Here slightly fewer infants of three to six months were being completely breast fed during the hunger-winter than before. On the other hand, the number of mothers supplying at least some milk to their infants was greater during the time of hunger.

Analyses made by Dr. J. H. P. Jonxis in Rotterdam<sup>21</sup> indicated that the milk produced by a few undernourished women showed no significant deviation from normal chemical structure. It is obvious that milk must often have been produced at the expense of the mother's own tissues, but no records by which the degree of such deficits could be measured were obtainable.

#### GENERAL COMMENT AND SUMMARY

The generalized undernutrition which occurred in Northwestern Holland during the winter of 1944-1945 was severe enough to interfere with the prenatal growth of infants born during that period. This was clearly shown for fetal weight, less definitely (but significantly) with regard to fetal length. Inasmuch as weight is a function of three dimensional growth while length is

but one dimension, this is not surprising. It is of interest that in the recent studies of Wallace<sup>22</sup> upon maternal undernutrition during late pregnancy in the sheep, the weights of newborn lambs were reduced by almost 50 per cent, while the lengths were much less sharply decreased. The decline of fetal growth, with its return to (and even beyond) previous normal levels after restoration of maternal food supply, indicate that the fetus is not independent of maternal diet. These findings testify to the actuality of the inadequate nutrition of pregnant women during the Dutch hunger-winter.

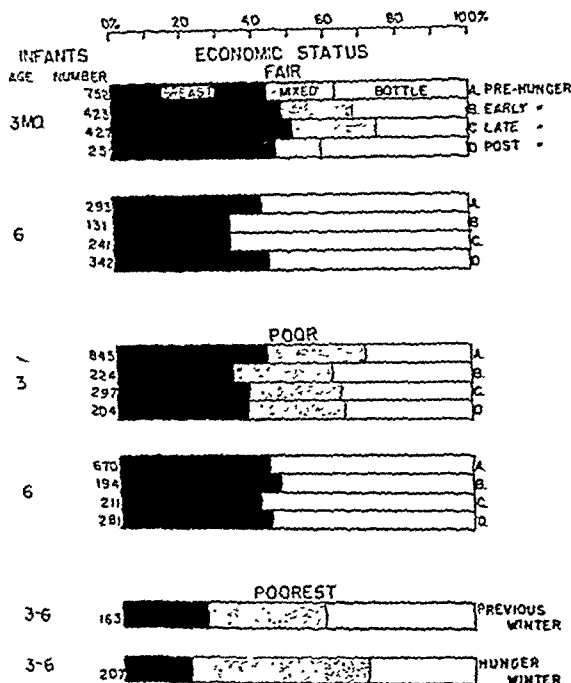


Fig. 4.—Percentages of clinic infants being breast fed at various periods before, during, and after the hunger-winter, according to economic status.

Under these circumstances menstruation ceased in about 50 per cent of urban women and became highly irregular in almost 50 per cent of the others. This is also presumable testimony to the degree of nutritional crisis. A result was the sharp decline in the number of births at appropriate later months.

Other effects must be presented with regard to their statistical reliability. For conclusions as to abortion and miscarriage, the available data were quite useless. The slight but statistically insignificant increase in premature birth appears to be founded upon serviceable figures. The frequency of stillbirth was definitely not increased. Data of dubious validity indicated that neonatal mortality was not increased. Congenital malformations, which appear irregularly in normal times, and are attributable to other factors not explored, were so slightly increased among the few conceptions occurring at the worst stage of undernutrition that the results in this regard are inconclusive. In any situa-

tion of sudden severe undernutrition similar to that which occurred in Holland, the almost predictable intervention of amenorrhea would, in fact, make the collection of useful statistics regarding fetal anomalies almost impossible. Lactation, considered solely as milk production sufficient to feed a baby, was evaluated well enough to indicate that the secretion of milk (in these limited terms) was not significantly influenced.

Perhaps the most important conclusion from consideration of the entire study is that nutrition, good or bad, is the sum of highly variable quantitative and chronologic factors. Total maternal undernutrition may well produce fetal effects entirely different from those of specific malnutrition associated with adequate intake of total calories. The results of any form of dietary inadequacy must vary in accordance with its extent in time, with the period of gestation in which it occurs, and especially with the duration of inadequacy before pregnancy. Only the most critical attitude toward all such matters and toward the social, economic, and genetic factors which may accompany improper food habits will clarify this very important subject. At present we still lack sufficient knowledge to say that deviations from the best possible maternal diet will inevitably lead to unsatisfactory results of pregnancy. Nor do we know to what degree proper maternal diet may be efficacious in producing uncomplicated pregnancies or more healthy infants at birth. The occurrences in Holland, however, add support to the accumulating evidence from animal experiments and human nutrition studies, that fetal growth may be retarded by lack of proper maternal diet.

#### CONCLUSIONS

During the six or seven months which preceded the liberation of northwestern Holland in May, 1945, a state of severe generalized undernutrition was prevalent in urban areas. The effects of this nutritional crisis upon the infant at birth were investigated especially in the cities of Rotterdam and The Hague. During the period, and apparently because of the low food supply, about 50 per cent of urban women became amenorrheic and presumably infertile. The birth weights of infants decreased, and rose after restoration of food, in a manner indicating that fetal weight gain is particularly related to the maternal diet of the last half or last trimester of pregnancy. Significant decline in birth length also occurred, but was less clearly apparent than the change in weight.

No conclusions could be drawn with regard to the frequency of abortion, while that of prematurity was insignificantly increased. Stillbirth was definitely not increased, nor was neonatal mortality among infants born in hospitals. The sharp fall in conception rate associated with amenorrhea resulted in so few pregnancies that data were inconclusive as to the relation between undernutrition in early pregnancy and malformation of the fetus. A slight but statistically insignificant increase in malformations did occur.

The percentage of mothers feeding their infants from the breast was not significantly altered during the hunger period.

Several of these results are so widely at variance with those of other studies as to indicate that great caution must be used in evaluating the maternal-fetal aspects of nutrition. Data as to the duration of maternal nutritional depletion and the specific dietary elements involved would appear to be of essential importance in any study of this problem.

Among the many persons in Holland who helped to make this investigation possible, thanks are especially due to Dr. A. van Ormondt of Amsterdam, Dr. J. H. P. Jonxis of Rotterdam, Professors E. Gorter and A. Holmer of Leiden, S. van Creveld and B. C. P. Jansen of Amsterdam, and K. de Snoo of Utrecht. Dr. C. Banning, Dr. Dols, and Dr. C. den Hartog of The Hague furnished many useful official statistics. Dr. J. Th. van der Hoeven was instrumental in locating infants for examination, and Miss D. Ten Haaf, the President of the Dutch Dietetic Association took the nutrition histories from their mothers, as well as performing many other useful services. Dr. J. Rietdijk, Miss Rijkenberg, and Dr. R. F. van Wering placed the records and facilities of the Midwifery School in Rotterdam completely at our disposal, as did the administrators of the Zuidwal Hospital at The Hague. Records were painstakingly transcribed by Miss Dini Kersteman, Miss M. Brandenberg, Drs. H. C. Rietdijk, and H. F. Begemann.

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# INFANTILE MORTALITY IN BUDAPEST IN THE YEAR 1945

AS REFLECTED BY THE MATERIAL OF THE CHILDREN'S  
CLINIC OF THE UNIVERSITY

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THE war is over, but the consequences of its privations are still to be felt keenly. Infantile mortality in Budapest in the past year reached really tragic dimensions. The data on mortality of the Children's Clinic of the University of Budapest reflect the extent of this national catastrophe. Last year, out of the 1,053 infants under one year of age admitted, 485 (46 per cent) died. Before giving a detailed account of this strikingly high death rate, it should be mentioned that during the whole year there was such a rush of patients in critical condition to the hospital that we had to admit quite a number of cases who died within the first twenty-four hours after admission. Owing to the high number of admissions, 1,053 in 1945, in comparison with 527 in 1942, we also had to disregard a good many hygienic considerations because of the overcrowding of the partially destroyed hospital.

Fig. 1 shows the role of the more frequent diseases in this strikingly high mortality rate. The data are compared with data from 1942, which might still be considered a peacetime year. The differences between the data of the two years might be considered to be the results of war privations. The less frequent diseases, congenital malformations, prematures, and, in general, diseases that bear no relation on the subject under discussion, have been omitted.

The height of each blackened column illustrates the per cent of the total number of infants admitted who died from the disease specified at the base of the column. This percentage can be compared to the data for 1942 (height of the unblackened columns).

The comparison of black and white columns shows immediately that the principal causes of the high mortality rate in 1945 are diarrhea and malnutrition. In 1945, we lost roughly ten times as many infants with diarrhea and five times as many with malnutrition as in earlier years. The cases booked under "diarrhea" were at the same time more or less severely malnourished, but the leading symptom was diarrhea. Clinically, the vast majority of the diarrheal cases could be considered cases of dysenteric infections; unfortunately, no bacteriologic analysis of the stools was possible in view of our wrecked laboratory. It is known, however, from experiences in earlier years, that the dysentery and especially pseudodysentery bacilli could be identified from the stools of similar diarrheal epidemics in about 90 per cent of all cases.

The only bright feature in the tragedy we are describing is the fact that in spite of the universal shortage of fuel material, respiratory infections did not appear in higher numbers than in previous years. The death rate in pneumonia, empyema, and otitis was even lower in 1945 than in 1942. The capital

with its thousands of undernourished children was fortunately spared from a great outbreak of epidemic respiratory infections. Such an outbreak would perhaps have practically wiped out all the infants spared or convalescent from dysentery.

Cases with "toxic" symptoms were, due to the higher frequency of diarrhea, comprehensively more numerous in 1945 than in earlier years.

Infections with pyogenic germs, such as septicemias increased in numbers as a corollary to malnutrition and bad sanitary conditions in general, such as lack of soap and linen.

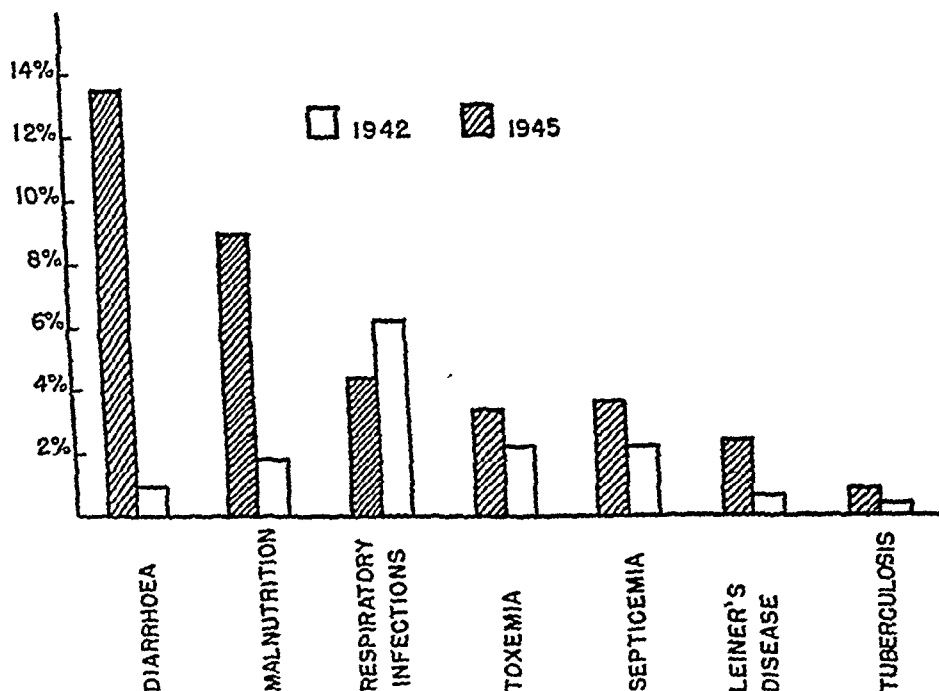


Fig. 1.—Mortality of certain diseases.

Quite an unexpected feature is the enormous frequency of cases of erythrodermia desquamativa of Leiner. We admitted four to six patients with this striking clinical picture every year, but the number of such admissions rose suddenly in 1945 to forty-five. We lost twenty-three of these. The increase in such cases might be connected with an unsatisfactory care of the skin (lack of oil, ointments, linen and soap). An infectious or deficiency factor could also, up to now, not be excluded from the etiology of Leiner's dermatitis.

The well-known postwar spreading of tuberculosis has not yet appeared to a great extent in our post-mortem material; we fear however, that the coming years will be worse.

Summing up the data described in Fig. 1, it is evident that the catastrophic increase in infantile mortality is to be attributed to diseases appearing regularly

every year in the capital. These well-known diseases, however, were more widely spread and caused a greater mortality in 1945 than ever before. The low resistance to these diseases is doubtless a result of the deficient nutrition of the infants. On the following pages will be described the extent and the causes of malnutrition.

The average weight at admission of the 1,053 infants analyzed in this paper was 26 per cent below normal (versus 10 per cent in 1942). This data is in itself indicative of the extent of malnutrition of the Budapest infants in 1945. As these infants had been fed almost exclusively, as will be described later, on a low protein, high carbohydrate diet ("Mehrnährschaden" of Czerny), the real extent of wasting was in many cases, due to starvation edema, unrevealed by the first weighing. As a sign of the loss of edema, the weight curve declined sharply after the first one or two weeks of adequate hospital diet and treatment with transfusions in a great number of cases. The real extent of malnutrition was accordingly greater than the average admission weight would indicate.

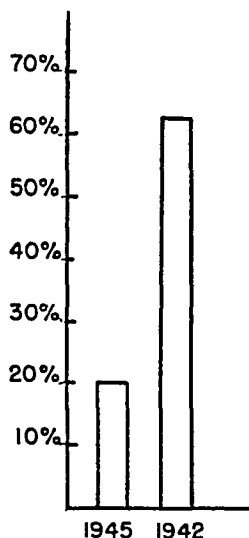


Fig. 2.—Percentage of infants breast fed on admission, 1924-1945.

Hand in hand with the malnutrition, rickets became almost universal. The deficiency of vitamin A was less marked, and cases with corneal ulcers were not observed. It is also interesting to point out that cases with manifest scurvy, a condition almost never observed in Hungary, did not appear in our material.

As to the origin of this unheard-of massing of malnutrition cases in Budapest, I will mention only a few facts. It is well known that cow's milk disappeared almost entirely from Budapest by the end of November, 1944, due to the approach of the battle front and the ruthless evacuation of cattle and food reserves by the defenders of the capital. The first scanty milk supplies appeared only a month after the siege, about the middle of March, 1945. By this time

every infant could receive 200 Gm. of milk. As the quality of this milk was, in spite of all efforts, strikingly bad, many mothers preferred to continue to feed their infants on milkfree diets. As powdered or evaporated milk were practically nonexistent, the formula generally used in the town consisted of a mixture of colloidal and crystalloid carbohydrates boiled in water with an occasional addition of traces of melted butter. In some exceptional cases, small additions of casein preparation were available. Beside this carbohydrate regime, older infants got some dried peas, potatoes, and exceptionally, carrots. Fruits did not come to the capital for almost half a year, and cod-liver oil, and vitamins were extremely scarce.

The situation briefly outlined above was greatly aggravated by the unlucky coincidence that the number of breast-fed infants declined sharply with the approach of the horrors of the siege. The milk production of the physically and morally exhausted, badly nourished mothers declined or even disappeared; the number of artificially, and comprehensively, inadequately fed infants increased steadily. Fig. 2 shows the extent of this misfortune as reflected on our admission material of 1945 compared to that of 1942.

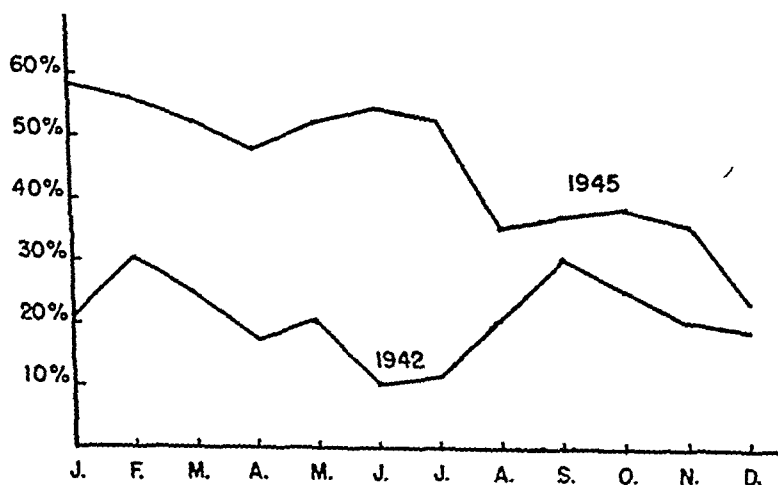


Fig. 3.—Mortality rate per month for 1942 and 1945 (calculated in percentage of monthly admissions).

The height of the white column shows the percentage of infants who had been breast-fed at admission and who could obtain women's milk in the clinic. (The figure is compiled only of data from the first seven months of 1945; later, conditions improved.)

I feel, that this decrease in the percentage of breast feeding, combined with the limited possibilities of artificial feeding, violating all the basic laws of pediatrics, explains the massed malnutrition in Budapest.

As to the origin of massed diarrheal disease, this had also been expected but could not be averted by our pediatricians under the given conditions. Dysentery is, as mentioned before, to a certain degree endemic in Budapest.



The great extent of the epidemic of 1945 seems to be explained by the following circumstances: cow's milk used for infant feeding should be, according to universally accepted, reasonable, pediatric standards, fresh, clean, unchanged, and free from preservatives. It should be free from pathogenic bacteria, and it should be used within twenty-four to forty-eight hours after milking. The disintegration of our milk collecting system, the breaking down of the communication system, the lack of ice, and the invasion of flies breeding in billions in the mountains of garbage and wreckage blocking the streets made it impossible to fulfill any of the postulates described before.

The increased mortality rate in Budapest is, as was demonstrated, a phenomenon that had to occur because of the unavoidable violation of well-known and well-established pediatric laws. As was mentioned before, conditions were such that the foreseen catastrophe could not be averted. We want to show, however, that help is possible, even with badly undernourished material, if optimal conditions can be realized. That was partially possible, if not for the community as a whole, at least for the Children's Clinic.

On the basis of prewar literature (Quest, Nobécourt) it is generally felt, that in cases of malnutrition, if the degree of wasting reaches 35 to 40 per cent of the average body weight, recovery is impossible. We found, however, in the latter half of 1945, having at this time an almost satisfactory supply of vitamins, drugs, women's milk and powdered milk at our disposal, that with the means mentioned above and with the help of blood and plasma transfusions continued daily for 10 to 20 days, quite a few cases reduced to 50 per cent, and some to 40 per cent of their ideal weight, could recover. The results of improved conditions and therapeutic possibilities in the second half of 1945 can be seen in Fig. 3.

In this figure the monthly mortality rate of the years 1945 and 1942 are plotted against each other. The data are calculated in per cent of the monthly number of admissions.

It can be seen from the figure that the mortality of the year 1945 begins to decline in the late summer and reaches almost the 1942 level by the end of the year. The average infant mortality of the clinic, even under peacetime conditions, is rather high. It varies in the neighborhood of around 20 per cent, the policy of the hospital being to admit only cases in a serious condition.

This reduction in mortality has been achieved, as was told before, by increased therapeutic facilities in the clinic, coming from various sources. By the end of July, the director of the Children's Clinic, Professor Paul de Kiss, obtained from the department of social welfare of the city of Budapest, food supplies to be exchanged for surplus milk of volunteering nursing mothers. This "milk bank" turned out to be a complete success; by the end of August every infant who needed it could get women's milk. At about the same time the International Red Cross put powdered milk at the disposal of the clinic in sufficient quantity to make artificial feeding safe and satisfactory. The chaotic financial status of the clinic was also somewhat relieved by gifts from the International Red Cross; damaged rooms could be repaired, remedying overcrowding. The same financial aid made it possible to give blood and plasma

transfusions on a larger scale than ever before. It should be mentioned here how hard it is to get volunteers for a series of ten to twenty blood transfusions in a half-starved community, if an adequate amount of food cannot be given to the volunteer. This point was, in our case, important, because a large part of the infants under our care had neither parents nor relatives. The medicine supply of the clinic also improved slowly in the second half of 1945. Help came from the International, the Swedish, and Danish Red Cross. Last but not least, the doctors of the American Military Mission, Colonels Shackleford and McClain, acquainted us with and taught us the use of penicillin.

By the end of 1945, we used penicillin in over twenty desperate cases, with unexpected results. This number has been increased now to over 140 cases.

Summing up the bitter facts presented in this paper, it is evident that the lowering of infantile mortality for the country as a whole is primarily not so much a medical as a social and financial problem. The availability of reliable or, if possible, condensed or dried milk in satisfactory amounts for the total population, together with a more ample supply of vitamins, soaps, oils, and linen, and the battle against flies, are the basis for a general campaign to lower infantile mortality. It is comprehensible that this goal cannot be attained fully without the restoration of our Children's hospitals to prewar efficiency.

## CHILDREN BORN DURING THE SIEGE OF LENINGRAD IN 1942

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THE extreme hardships endured by the people of Leningrad during the siege of that city by the Germans from 1941 to 1943 were bound to affect the health of the women, the course of their pregnancy and confinement, and the condition of their newborn children.

The material presented here is based on records of the Department for the Newborn of the Leningrad State Pediatric Institute. It deals primarily with children born during the siege in 1942. (The Siege of Leningrad lasted altogether from August, 1941, to January, 1943. Conditions were especially severe from the city's encirclement in September, 1941, until pressure was eased somewhat in February, 1942.) Though this material is incomplete and has many defects, it is felt that its publication is justified. Though it fails to answer many questions, factual material obtained under exceptional conditions is useful for comparison and in this instance has some historic value. As to its incompleteness, the material was collected by people who lived under great difficulties, and should not be judged too strictly.

Incessant bombing from the air, shelling from long-range guns, fires, air-raid alarms by day and night all had their effect on the nervous systems of the women. Without stopping daily work for a minute, the whole population took part in improving the city's defenses. Houses were without heat, and the winter of 1941-1942 was unusually severe. There was no transportation. On a diet hardly sufficient to keep them alive, the women had to undergo physical exertions to which many of them had not been accustomed, such as standing in long lines for bread and other things in the biting cold and often at night, walking long distances, sometimes with heavy loads, chopping wood, clearing snow and ice, cleaning back yards, and standing guard during the long cold nights at entrances to buildings or on roofs in the frequent air raids.

The people suffered from hunger because food was insufficient in quantity and inferior in quality. The mortality rate was high. Cases of alimentary dystrophy increased greatly. Food conditions during this part of the siege can be judged from the rations of bread, at that time the principal food. The daily allowance of bread from September, 1941, to February, 1942, was as follows:

During month of—	Ration for manual workers	Ration for mental workers
	(Gm.)	(Gm.)
September, 1941	500	300
October, 1941	400	200
November, 1941	300	150
December, 1941	250-350	125-200
January, 1942	400	300
February, 1942	500	400

Translated from the Russian.

Not only were the rations small, but the nutritional value of the bread was low, for it consisted of about one-half defective rye flour, the rest being substitutes such as cellulose, malt, and bran.

Thus, hunger, vitamin deficiency, cold, excessive physical strain, lack of rest, and constant nervous tension had their effect on the health of the women, the intrauterine development of the fetuses, and the condition of the newborn children during the siege.

*General Information on Children Born in 1942.*—General information on babies born in 1942 is given in Table I. In the first six months, 414 women entered the clinic; in the second half of the year, only seventy-nine, owing to the sharp fall in the birth rate in Leningrad. Aside from the numerical difference, the mere fact that a number of women became pregnant and bore children at a time when amenorrhea was widely prevalent suggests analysis of the figures for the second half of 1942 separately from those for the first half.

TABLE I. BIRTHS AND NEONATAL DEATHS FOR THE YEAR 1942

	NUMBER DURING PERIOD		
	JANUARY TO JUNE	JULY TO DECEMBER	YEAR 1942
<i>Births</i>			
Live births:			
Born at term	230	72	302
Born prematurely	161 (41.2%*)	5 (6.5%*)	166 (35.5%*)
Total live births	391	77	468
Stillbirths	23 (5.6%†)	2 (2.5†)	25 (5.1%†)
Total, all births	414	79	493
<i>Neonatal deaths</i>			
Of babies born at term	21 (9%‡)	1 (1.4%‡)	22 (7.3%‡)
Of babies born prematurely	62 (30.8%§)	3 (60%§)	65 (39%§)
Total neonatal deaths	83 (21.2%*)	4 (5.2%*)	87 (18.6%*)
Total loss in children (stillbirths plus neonatal deaths).	106 (25.6%†)	6 (7%†)	112 (22.7%†)

\*Per cent of live births for same period.

†Per cent of all births for same period.

‡Per cent of live births at term for same period.

§Per cent of premature live births for same period.

TABLE II. LIVE BIRTHS AND STILLBIRTHS, 1939 TO 1942

YEAR	NUMBER						RATIO OF STILLBIRTHS TO ALL BIRTHS FOR SAME PERIOD (%)		
	LIVE BIRTHS			STILLBIRTHS			JAN- UARY TO JUNE	JULY TO DECEM- BER	ENTIRE YEAR
	JAN- UARY TO JUNE	JULY TO DECEM- BER	ENTIRE YEAR	JAN- UARY TO JUNE	JULY TO DECEM- BER	ENTIRE YEAR			
1939	2,014	1,958	3,972	51	52	103	2.50	2.66	2.52
1940	2,685	1,639	4,274	72	40	112	2.73	2.44	2.55
1941	2,007	1,049	3,056	49	34	83	2.44	3.24	2.64
1942	391	77	468	23	2	25	5.55	2.53	5.07

Premature births in the first half of 1942 reached the high proportion of 41.2 per cent; in the second half the proportion was only 6.5 per cent, which differs little from the normal rate. The proportion of stillbirths also was exceptionally high in the first half of the year (5.6 per cent) while in the second half it was 2.5 per cent, which is within normal limits as can be seen in Table II.

How did the seventy-nine women who entered the clinic in the second half of 1942 differ from the other women in Leningrad, so that they did not suffer from amenorrhea and were able to become pregnant, and so that the proportions of stillbirths and of premature births among them were not above the normal? While the material is too limited for positive answer, there are reasons to believe that their nutrition was much better than that of the rest of the women in the city during that period. It was possible to ascertain that among these seventy-nine women, fourteen were employed in food industries (cooks, waitresses, and others), six were receiving military rations, seventeen were physicians, nurses, teachers, and members of other professions, fourteen were manual workers, and twenty-two were housewives. Had information been obtained about the occupations of the husbands of the twenty-two housewives, it would doubtless have strengthened further the assumption that the food of the women who bore children in the second half of 1942 was considerably better than that of the other women in the city. In any event, these seventy-nine women did not suffer from the hunger that was the lot of the others.

On the other hand, it seems obvious that the cause of the unusually high proportions of premature births and of stillbirths in the first half of 1942 was hunger during pregnancy, that is, the insufficient quantity and the unsatisfactory quality (lack of vitamins) of the women's food.

*Average Birth Weight of Children Born in 1942.*—In dividing the newborn children into those born at term and those born prematurely, one should not be guided by one symptom but should consider, for each child, the obstetric history together with the baby's length and weight and the general morphologic data. But since the obstetric history is not always available nor always reliable, and since the weight of the newborn can hardly be taken as an indicator of his maturity or prematurity when the mother suffered from hunger during her pregnancy, we have preferred to take the length of the newborn as a more stable and sufficiently objective sign. Accordingly, we have placed in the category of children born at term those whose lengths at birth were 47 cm. or more, irrespective of weight, and we have classed as premature those less than 47 cm. long at birth.

In considering the children according to weight at birth, we found that they grouped as follows:

<i>Weight at birth:</i>	<i>Number</i>	<i>Per cent</i>
Less than 2,000 Gm.	77	20.9
From 2,000 to 2,500 Gm.	104	28.2
From 2,500 to 3,000 Gm.	118	32.1
From 3,000 to 3,500 Gm.	56	15.2
From 3,500 to 4,000 Gm.	12	3.3
Over 4,000 Gm.	1	.3
Total	368	100.0

The number of children with low birth weights was striking. Of those born in the first half of 1942, 49.1 per cent weighed less than 2,500 Gm., and only 4 per cent weighed more than 3,500 Gm. As can be seen from Table III, even

TABLE III. AVERAGE WEIGHT AT BIRTH OF INFANTS BORN AT TERM

PERIOD	AVERAGE WEIGHT AT BIRTH (GM.)		NUMBER INCLUDED IN COMPUTATION OF AVERAGE	
	BOYS	GIRLS	BOYS	GIRLS
January-June, 1941	3,444	3,302	933	874
July-December, 1941	3,344	3,222	503	447
January-June, 1942	2,815	2,760	135	120
July-December, 1942	3,199	2,890	39	32

in the latter half of 1941 it was possible to observe a slight decrease, about 100 Gm., in the average birth weight. That decrease is attributed to the deterioration of the diet and general living conditions in the beginning of the siege, when the pregnancies of the women who bore children in the second half of 1941 were near an end. The fall in the average birth weight was much greater in the first half of 1942, that is, among the children of women who suffered from hunger during all or nearly all of their periods of pregnancy.

The average birth weight of boys carried to term in the first half of 1942 was 529 Gm. less than in the last half of 1941, and of girls it was 542 Gm. less. Though our material is not extensive, there is no doubt about the reliability of these figures, inasmuch as an almost equal decrease in average birth weight of children carried to term was observed in other maternity clinics in Leningrad. In the Snegirev clinic, the average decrease was 500 Gm.<sup>1</sup> In the obstetric-gynecologic clinic of the Second Leningrad Medical Institute the average birth weight in 1942 was 410 Gm. less than in 1940.<sup>2</sup>

From Table III it can be seen that the average birth weight increased considerably in the second half of 1942, though it was still noticeably below normal. This increase apparently should be attributed not so much to improvement in food conditions of the Leningrad population as a whole (although no doubt there was some general improvement) as to the fact already brought out that a large proportion of the women who bore children in the second half of 1942 were receiving considerably better food than the other women in Leningrad.

*Physiologic Loss of Weight in Children Born at Term.*—In 1918, on the basis of many observations of the effect of hunger on lactation in women, we came to the following conclusions:<sup>3</sup> (1) in spite of hunger, the mammary gland secretes milk if there is sufficient physiologic stimulation, that is, the capacity for breast feeding remains; (2) the quantity of milk, however, decreases; and (3) the duration of the lactation period becomes shorter. These circumstances were observed also during the siege of Leningrad, 1941 to 1943, with the difference that the mother's incapacity to produce sufficient milk was greater.

The extent and duration of the physiologic loss of weight and the rapidity of restoration to the initial weight depend mainly upon food conditions, that is, on the quantity of the mother's milk; to some extent they probably depend also upon the strength with which the child sucks, that is, on his general vigor. Most of the children born late in 1941 and in the first half of 1942 of severely exhausted mothers had very low vitality. The mothers as a rule had very little milk, and many babies had to be fed, even in the first few days of their lives, on artificial mixtures prepared from milk substitutes because there was no cow's milk.

Data on the physiologic loss of weight in children born at term (with a length of 47 cm. or more) in 1942 are given in Table IV, except for those who died while still at the clinic and for those whose mothers returned to their homes on or before the fourth day after the birth.

TABLE IV. PHYSIOLOGIC LOSS OF WEIGHT IN NEWBORN CHILDREN DURING 1942

AGE	NUMBER	WEIGHT (GM.)	LOSS OF WEIGHT, (GM.)
At birth	212	2,808	--
Second day	177	2,723	-85
Third day	199	2,643	-80
Fourth day	188	2,599	-44
Fifth day	161	2,590	- 9
Sixth day	125	2,535	-55
Seventh day	104	2,577	+42

The loss of weight lasted three days or less in only 11.2 per cent of the children; in 88.8 per cent it lasted more than three days. Many of the children were discharged without any established tendency toward further gain in weight. On the average, the loss of weight continued for six days instead of three to four days; the average loss was 273 Gm., 9.7 per cent of the original weight.

*Clinical Characteristics.*—The most noticeable characteristic of the newborn children in the first half of 1942 was their low vitality. Most of them were inert from time of birth; they did not maintain their temperature satisfactorily and became chilled easily; their sucking at the breast was weak; they had little resistance to all outside harmful influences. This general functional insufficiency was favorable to the development of various diseases that ended fatally after brief courses. In some newborn children it was possible to see a highly colored physiologic erythema, which in most cases remained very long (four to seven and even eleven to fifteen days). On the other hand, cases of so-called toxic erythema of the newborn were observed rarely. According to Vogt, this is generally found in almost 50 per cent of the newborn. We too had observed this condition very often in normal times, though we never attempted to determine its frequency.

In the first six months of 1942 we observed erythema in six of the 391 newborn children, about 1.5 per cent. In the second half of that year, there were eleven cases among the seventy-seven infants, or fourteen per cent. If toxic erythema is to be considered an allergic condition, its disappearance evidently should be attributed to the absence, from the food of the hungering mother, of some substances (possibly albumins) that produce sensitization in the child's body and bring about this rash.

Swelling of the mammary glands, usually found in 95 per cent of the newborn and very pronounced in 1.5 per cent, was observed in the first half of 1942 in only nine of the 391 newborn children, or 2.3 per cent. On the other hand, we observed quite often a congenital softening of the bones of the skull, open sutures, and very wide fontanels, which in former times were rare.

Our data about the greater frequency of stillbirths and premature births, the low birth weights, the lowered vitality of the newborn children, and the

changes in their bones, agree closely with data obtained in experiments on animals subjected to severe hunger. Therefore, although we are unable to determine the exact difference between the food ration of our starving mothers and a normal diet, it is possible to conclude on the basis of the courses of their pregnancies and the condition of their newborn children that they had been subjected to severe hunger both quantitative and qualitative.

*Morbidity and Mortality.*—The morbidity of children born in 1942 was very high, 32.3 per cent. In the first half of the year it was 33.5 per cent; in the second half, 27.1 per cent. Scleredema and sclerema were most frequent, particularly in the first semester, with fifty-three cases; next was pneumonia, with fifty-one. There were ten cases of intracranial hemorrhage. Most of the cases of scleredema and pneumonia were fatal, particularly when the two were combined.

The mortality of children born in 1942, particularly in the first half of the year, was unusually high. Of the 391 children born alive in the first half, eighty-three (21.2 per cent) died in that period; twenty-one (9 per cent) of the 230 infants born at term and sixty-two (30.8 per cent) of the 161 premature infants died.

An equally high, or even higher, mortality of the newborn was observed in the other maternity homes of Leningrad. In the obstetric clinic of the First Medical Institute, the neonatal mortality in 1942 was 5.6 per cent for those born at term and 44.2 per cent for premature infants. For the city as a whole, the mortality of infants born at term was nowhere less than 12 per cent and in some institutions as high as 31.9 per cent. For the premature infants the range was from 50 per cent to 80 per cent.<sup>2</sup>

The main causes of death were: pneumonia in thirty-one cases; pneumonia combined with scleredema in seventeen; scleredema in ten; intracranial hemorrhages in nine; prematurity and congenital debility in eleven; other causes in four; unknown causes in five. It must be stated, however, that in the eighty-seven deaths the causes were determined by pathologic examination in only seven cases, because the autopsy room did not function during the entire winter of 1941-42 on account of lack of water, fuel, and for other reasons.

Regarding prematurity and congenital debility as causes of death, these diagnoses were found many times in reports of autopsies not only in 1942 but also in 1943, in spite of the fact that the Department of Pathology and Anatomy of the Institute tried hard to avoid such indefinite diagnoses. In many cases the pathologists and anatomists were unable to ascertain more accurately the cause of death. Clinically, these infants presented a very definite picture of general congenital debility.

The mortality rate from pneumonia and scleredema is attributed to the conditions under which the clinic was operating in the winter of 1941-1942.

*Department for the Newborn During the Siege.*—In the beginning of the war the Department for the Newborn consisted of 120 beds and was situated on the third floor of the obstetric-gynecologic building. During air raids the babies were taken by elevator to the basement, where an air-raid shelter was specially



equipped for them. Late in the fall of 1941, damage to the central heating plant forced the obstetric department to move, with reduced facilities, to other quarters which could be heated by stoves. The Department for the Newborn was placed in a ward of fifteen to twenty beds, which was heated by a brick stove with a pipe connected to a window. The stove was too small to heat the ward adequately; it smoked often, and there was not enough wood. The temperature in the ward was usually very low, often 50° F.; in the fourth week of January, 1942, it went down to 40° F. The physicians and nurses worked in their overcoats (over which they wore white coats) and in felt boots. Medical examination of the infants and changing of diapers brought danger of chilling. The same danger threatened in the corridor and in the mothers' ward, where the infants were taken for feeding and where the temperature was lower still. The situation was made worse by the insufficiency of heaters, the impossibility of repairing damaged heaters, and the insufficiency of hot water (the water system was not working; water could be heated only on the stoves in the wards). It is not surprising that during that time many newborn infants died from such diseases as scleredema, sclerema, and pneumonia. It should be added that of the children born at home the majority were brought to the clinic severely chilled.

The large number of premature births, the congenital debility of many babies born at term but with low weight, and poor conditions of care and feeding, all explain the high neonatal mortality at the end of 1941 and in 1942. Under these difficult conditions, the staff of the Department for the Newborn, Dr. R. M. Levis and the nurses, themselves in a condition of advanced alimentary dystrophy, did everything they could to preserve the lives of the newborn babies; but, unfortunately, many things did not depend upon their good will and devotion.

*Weight of Newborn Children.*—The effect of hunger of the pregnant woman on the weight of the newborn child was discussed at the end of the war of 1914-1918. Contradictory opinions were expressed. The majority of the writers concluded that the mother's insufficient food during the war had no noticeable effect on the weight of the newborn child, and that there were no "war babies" with a definitely lower birth weight (Richter, Kütting, Tschierch, Ruge, Bruce, Murray, and others).

Other authors, however, noted that insufficient food of pregnant mothers had brought about a slight decrease in the average weight of newborn babies. According to Hamm this decrease was 32 Gm.; Hecker, 50 Gm.; Schauta, 80 Gm.; Bickhoff, 100 Gm.; David 95, Gm. (3 per cent); Binz, 3 per cent; and Peller, 11 per cent. Peller and Bass expressed the opinion that in hungry mothers there was a compensatory lengthening of pregnancy and the decrease was therefore comparatively small. That opinion was rejected by David, according to whose data the duration of pregnancy, whether in wartime or peacetime, was, on the average, 273 days. Some writers, among them Brüning, found that in the war of 1914-1918 the proportion of newborn babies of normal weight and above normal not only failed to decrease but even showed some increase.

The contradictory results of these studies can be explained by the fact that living conditions and food are not the same in all localities of the same country; they are better in some places and worse in others.

Is it surprising that in England (Bruce and Murray) the war years did not affect noticeably the birth weight of babies? Can it be said that the people of England or Germany really suffered from *hunger* in the years 1914-1918? There was some deterioration of general living conditions and some food shortages among certain parts of the population, but there was no hunger. This circumstance explains why the majority of authors came to the conclusion that the diet of the pregnant woman had either no effect on the weight of the newborn baby or only a very slight effect.

Among the Russian writers the conclusions are less contradictory and more definite than those of the English and German writers. According to Shkarin,<sup>4</sup> the proportion of babies with birth weights above the average (more than 4,000 Gm.) was lower in 1919 than in 1913, while the proportion with very small birth weights (below 2,300 Gm.) was higher. Lurie and Belugin<sup>5</sup> found that with insufficient diet there was a slight decrease in birth weight, in 1919 the average birth weight was 160 Gm. less than in 1915. According to Troitzkaia,<sup>6</sup> the average birth weight in 1919 was 200 Gm. less than in 1914. This did not prevent either Troitzkaia or Lurie and Belugin from reaching the conclusion that the fetus receives from the mother's body everything it needs for its development, regardless of the nourishment received by the mother from the outside, that, in other words, the fetus behaves like a parasite.

According to Lichkus and Valitzki,<sup>7</sup> the average birth weight of children carried to term was 3,485 Gm. in 1911 and 3,269 Gm. in 1919, a decrease of nearly 200 Gm. or 5.7 per cent. Gershenson<sup>8</sup> found that the average birth weight of children of primiparas in Odessa in the famine years 1921-1922 was 112 to 113 Gm. below that in the prosperous years 1924-1926; for children of multiparas the difference was 210 to 258 Gm. Gershenson rejects the theory that the fetus is a parasite, and considers that the mother's exhaustion caused by insufficient food (possibly combined with serious emotional disturbances) results in a considerable lowering of the birth weight. Treiter<sup>9</sup> states that the average birth weight in Viatka in the famine year of 1920 was 3,107 Gm. or almost 100 Gm. lower than the average of 3,200 Gm. in 1913, a prosperous year.

Thus, the Russian writers, while differing somewhat in the evaluation of their factual material, came to the fairly unanimous conclusion that the insufficient diet of pregnant women results in a lowering of the average birth weight of their children. The data on the weight of newborn children given by foreign writers do not agree with those of Russian writers, but both coincide with the results of animal experimentation on the effects of the mother's hunger on the fetus.

On the basis of his experiments, Rudolski<sup>10</sup> thinks that a general decrease in the pregnant female's food not only may bring about insufficient general development of the fetus and low vitality, but also may affect some special tissue, as, for instance, that of the bones. "The young of hungering female

animals," he states, "differ greatly in their appearance from those of normal females, particularly in cases of medium and severe degrees of hunger; the young lack teeth, their integuments are transparent, their subcutaneous fat is poorly developed, and their bones are soft and flexible." A decrease in the size of some young and the above-stated changes in them were observed by Rudolski only when the starving mothers' food ration was cut to one-fifth or less of its normal size. When the female rabbit's food ration was cut to one-half and the dog's ration to one-third the young were of normal size.

In conclusion, the results of our clinical observations agree with the results of experiments on the effect of hunger of pregnant animals on their young. If the hunger during pregnancy does not exceed certain limits, it does not noticeably affect the development of the fetus, which is able to extract from the mother's body whatever it needs for normal development. However, if the hunger has reached a severe stage, it invariably affects the development of the fetus by producing stillbirths, a large percentage of premature children, a sharp decrease in the average birth weight, and a large number of children born with low vitality.

#### SUMMARY

1. The severe quantitative and qualitative hunger from which the women of Leningrad suffered during the siege affected the courses and results of their pregnancies and the condition of their newborn children.

2. During the particularly severe hunger in the first half of 1942, the still-birth rate rose to 5.6 per cent, twice the normal figure; the rate of premature births reached the unusually high figure of 41.2 per cent.

3. There was a great decrease in the proportion of children born at term with heavy weights, and conversely a considerable increase in the proportion of lightweight children.

4. The average weight of infants born at term in the first half of 1942 was 500 to 600 Gm. less than normal.

5. The physiologic loss of weight continued longer than usual; the average loss exceeded the usual figure.

6. Of the clinical characteristics of the newborn infants, the following were noteworthy:

- a. Generally lowered vitality.

- b. Brightly colored, physiologic erythema, which in some infants continued for a long time.

- c. Rare occurrence of toxic erythema of the newborn.

- d. Rare physiologic swelling of the mammary glands.

- e. Frequent congenital softening of the skull bones.

7. The morbidity of the newborn was unusually high, 32.3 per cent, owing in part no doubt to their low vitality. The most frequent diseases were sclerodema, sclerema, and pneumonia.

8. The mortality of the newborn was unusually high, 9 per cent for those born at term and 30.8 per cent for those born prematurely. This too should be attributed to a certain extent to the low vitality of many of the children.

9. The capacity for breast feeding remained even in severe degrees of hunger, but less milk was produced and the breast feeding period was considerably shorter.

10. While, in general, we do not contradict the prevailing opinion that the fetus behaves like a parasite in the mother's body, we can say on the basis of our material that the condition of the host, the mother's body, is of great consequence to the fetus, and that severe quantitative and qualitative hunger of the mother decidedly affects the development of the fetus and the vitality of the newborn child.

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## AIRBLOCK IN THE NEWBORN INFANT

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THE condition produced by escape of air from the normal respiratory pathways into tissues in which it is not normally present may frequently become very serious. For this reason a previous author<sup>1</sup> believes that it deserves a name and has used the term airblock. To us this term seems accurate, descriptive, and adequate; we have, therefore, employed it.

Our earlier report on this condition in the newborn period<sup>2</sup> suggested to us that a more accurate appraisal might be possible after we had observed a series of patients who came to necropsy. The post-mortem examinations in the six cases herein reported were performed by four different pathologists. In order to obtain a thorough review of all cases we have asked the third author, a pathologist, to participate in this study.

Since some of the terms used are awkwardly long, we have substituted the abbreviation PIE for pulmonary interstitial emphysema, ME for mediastinal emphysema, and PT for pneumothorax. The use of such abbreviations in a discussion of airblock is not without precedent.<sup>3</sup>

### METHODS OF POST-MORTEM EXAMINATION

It is our belief that airblock is frequently unappreciated at autopsy. Aberrant air may not be detected by the usual methods of examination, and its presence and importance are likely to be appreciated only if the pathologist has airblock in mind. Davis and Stevens<sup>4</sup> reported finding six patients with PT in routine roentgenographic examination of 702 consecutive newborn infants, an incidence of approximately one per cent. PT, then, might be expected to exist in one per cent of all newborn infants coming to necropsy, regardless of the cause of death. Since PT and ME are extensions of PIE, the last should be even more common. Moreover, airblock alone may prove fatal. This suggests that air outside of the normal respiratory pathways is present in considerably *more* than one per cent of all newborn infants coming to necropsy. When one considers the careful examination by the pathologist to detect other conditions which may be present in no more than one-tenth of one per cent of newborn infants, the belief that aberrant air frequently does not receive its due consideration seems justified.

The most reliable method of demonstrating PT at autopsy is to enter the pleural spaces under water. We believe that this should be a part of the routine post-mortem examination of newborn infants. It is our practice to enter the pleural spaces with the entire infant submerged in water, being careful not to damage the visceral pleura. The pericardial space should be entered

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similarly. Although ME is usually quite evident if present, it is advisable that the sternal plate be removed while the infant is still submerged. Before the thoracic viscera are disturbed, each lung should be gently lifted forward and the posterior mediastinum inspected for emphysema.

We have had no experience with Hartroft and Macklin's method of reinflating the lung with an intrabronchial fixative.<sup>5</sup> However, in cases other than those reported here, we have ligated the trachea before entering the thorax so as to avoid the loss of air occasioned by collapse of the fresh lungs. In the patients with more severe PIE there are likely to be subpleural blebs of air, varying in size up to more than one centimeter in diameter. These blebs of air are in the interstitial tissue; they are not dilated alveoli nor congenitally large air sacs. If these are not visible in the fresh state, they may appear if the entire, uncut lungs are subjected to fixation in 10 per cent formalin. We have discovered this in patients with PIE seen since the last one reported here. Similarly, PIE present deeper in the lung is more easily demonstrable if the entire lungs are fixed before they are cut. A very satisfactory manner of examining the cut surface of the fixed lung for PIE is to use a binocular dissecting microscope which provides a magnification that can be varied from about  $\times 12$  to  $\times 36$ . In this way a view may be obtained of tissue masses too large to be satisfactorily sectioned and stained. Also, the tissues are thus examined before being subjected to the further distortion and shrinkage involved in the preparation of stained sections. It provides an important link between gross examination and microscopic examination of prepared sections, by means of which the latter may be more satisfactorily interpreted. Occasional findings, which may be possible artifacts or post-mortem changes, can sometimes be more accurately interpreted by the presence of hemorrhage resulting from PIE.

Although we thought occasional sections suggested the presence of air inside both blood vessels and dilated, torn lymph channels, these findings were not recorded in the autopsy protocols, since our patients were not examined for air embolism. It is probable that such an examination should be a routine part of the autopsy of these patients. Joannides and Tsoulos<sup>6</sup> found air in the cardiac chambers and general circulation in 80 per cent of dogs that developed experimentally produced PIE. Others<sup>4, 7</sup> have noted air in the vascular system following similar experiments.

Although in one of our patients the fresh lungs were reinflated with air below water in an effort to detect the escape of air either through the visceral pleura or at the mediastinum, we do not think that the reinflation was performed in a satisfactory manner. Therefore, this was omitted from the autopsy protocols. Such a procedure is valueless unless a manometer is used to ascertain the amount of pressure employed. It must also be borne in mind that the act of reinflation may itself produce PIE and impair the value of subsequent examination. However, demonstrating a break in the visceral pleura by purely anatomical means is very difficult and often unreliable. For this reason we attach little value to an apparent rupture of the pleura as evidenced by stained microscopic sections.

## CASE REPORTS

**CASE 1.**—Infant S., a boy, was born Aug. 12, 1943, at 6:30 A.M., at Hermann Hospital, weighing 3,300 Gm. Delivery was spontaneous of a 28-year-old white woman, gravida 4, para 3. Position was left occipitoanterior. The first two stages of labor lasted about twelve hours. The mother received nitrous oxide and ether during delivery. The infant appeared weak and feeble, and respiration was established with difficulty using a tracheal catheter, carbon dioxide-oxygen inhalations, Metrazol, and artificial respiration (type not recorded). Physical examination showed pallor, cyanosis, and labored respiration. Both lungs were full of fine, sticky râles. Cry was absent. The infant was given continuous inhalations of 5 per cent carbon dioxide and 95 per cent oxygen.

During the day respiration continued shallow and labored and color poor. At 10:00 A.M. anteroposterior and right lateral roentgenograms of the chest were made. These films are illustrated in Fig. 1. The infant expired at 7:05 P.M.

*Post-mortem examination.*—The pleural spaces were carefully entered under water and a considerable amount of air escaped from the right. No air escaped from the left pleural space. There was no ME. Numerous subpleural blebs of air were present on all lobes of the right lung. The uncut lungs were not subjected to fixation. The lungs were not examined with a dissecting microscope.

Since most of the histologic findings in all patients (except in Case 4) were similar, the findings in this patient will be used as a basic description. Brief comparative descriptions will be given in the subsequent cases. Similarly, Figs. 9, 13, and 14 may be taken as illustrative of all cases (except Case 4).

Sections for microscopic examination were made from two areas. The sites from which the blocks were taken are not known. The largest bronchus had a wrinkled lining. In the lumen there was a long, slender cord of fibrin, desquamated mucosa, and a few erythrocytes and granulocytes. The smaller bronchi contained masses of fibrin which sometimes contained incorporated neutrophiles. Many of the bronchi and bronchioles were completely filled with amniotic fluid debris. Only a few of the small bronchioles were intact. Most were markedly dilated and filled with keratinized epithelium, erythrocytes, neutrophiles, and occasionally masses of fibrin. Frequently the bronchiolar wall formed a small segment of the wall of an irregular defect filled either with blood or amniotic fluid debris. Some of the spaces were partially empty. Others were lined with a thick layer of fibrin.

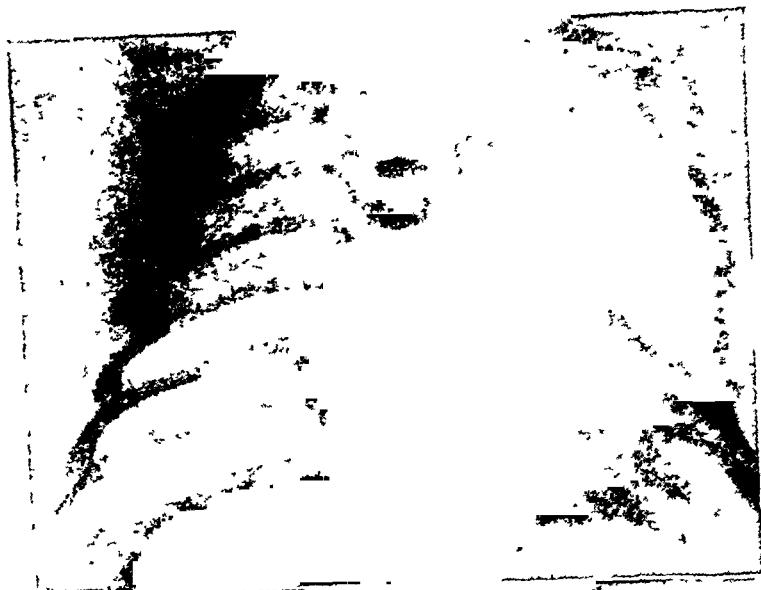
Very few alveoli contained air. The alveolar walls were markedly congested. There were large areas of hemorrhage and areas of collapsed alveoli. In small foci the air spaces were filled with neutrophiles. Scattered through the sections were round, ovoid, or dumb-bell shaped defects with compressed linings. Frequently, the spaces consisted partially or entirely of markedly dilated bronchioles.

Long, wide, shredded defects, which contained varying amounts of blood, extended along the septa into the pleura. Most contained only small amounts of blood, but elongated hemorrhages were noted in the septa and pleura. Irregular defects, sometimes occurring in successive layers, were noted around large blood vessels and bronchi. Some of these structures were almost completely detached from the surrounding tissues. Similar tears were noted around smaller blood vessels. In addition, there were ovoid spaces with smooth linings which closely resembled markedly dilated capillaries, occurring particularly around medium sized vessels. Some of the blood vessels were markedly congested. Others were collapsed and contained little blood. Sometimes the blood only partially filled the lumen.

The remainder of the examination was essentially negative. There was neither cervical nor retroperitoneal emphysema. The cranial cavity was not entered.

**CASE 2.**—Infant S., a white girl, was born Oct. 27, 1943, at 2:15 P.M., weighing 3,000 Gm. Labor was complicated by prolapse of the umbilical cord, and the infant was delivered by version and extraction. Resuscitation was very difficult and included the use of a tracheal catheter and two intracardiac injections of epinephrine. After an hour the infant's color

A.



B.

Fig. 1.—A, Case 1. AP view with the infant lying on his back. There is atelectasis of the left upper lobe. There is marked emphysema of the right lung and probably of the left lower lobe. There is a small right PT. The margin of the right lung is discernible in the region of the right upper thorax. Either the air in the right pleural space, or the emphysematous right lung, seems to extend across the midline to the left of the vertebral column. This probably explains the substernal collection of air seen in the left lateral view.

B, Lateral view with the infant lying on his left side. There is a large collection of substernal air. This substernal air is seemingly in the anterior mediastinal space. This, however, is probably air in the right pleural sac herniating across the midline in the anterior mediastinal space (See Fig. 1, A). Post-mortem examination showed a right PT and extensive right PIE, but no ME.



improved except for occasional attacks of cyanosis. Moist râles could be heard throughout both lungs. In a few hours continuous cyanosis recurred, accompanied by dyspnea. At the age of 5 hours a left PT was diagnosed.

At the age of 7 hours the infant was admitted to the St. Louis Children's Hospital. Physical examination showed dyspnea, cyanosis in spite of continuous administration of oxygen, and signs typical of left PT, including shift of the heart to the right. Fluoroscopy showed a partial left PT (about 50 per cent), with shift of the heart to the right of the sternum. A left thoracentesis obtained 50 c.c. of air. Following this the infant seemed to improve, and fluoroscopy showed the amount of PT to be decreased and the heart in a normal position. During this period of time both epinephrine and Coramine had been administered subcutaneously.

At the age of 10 hours, dyspnea and cyanosis recurred. A left thoracentesis was repeated, but this time it was found impossible to reduce the amount of air in the left pleural space: the PT was under considerable tension, and air apparently entered as rapidly as it could be aspirated.

At the age of 12 hours a closed left thoracotomy was performed and the catheter connected to a water trap. Air bubbled out with each expiration. Following this procedure the cyanosis disappeared, but the dyspnea continued. Finally, breathing became irregular with long periods of apnea. More epinephrine and coramine were administered subcutaneously. The infant expired at 6:15 A.M., October 28, at the age of 16 hours.

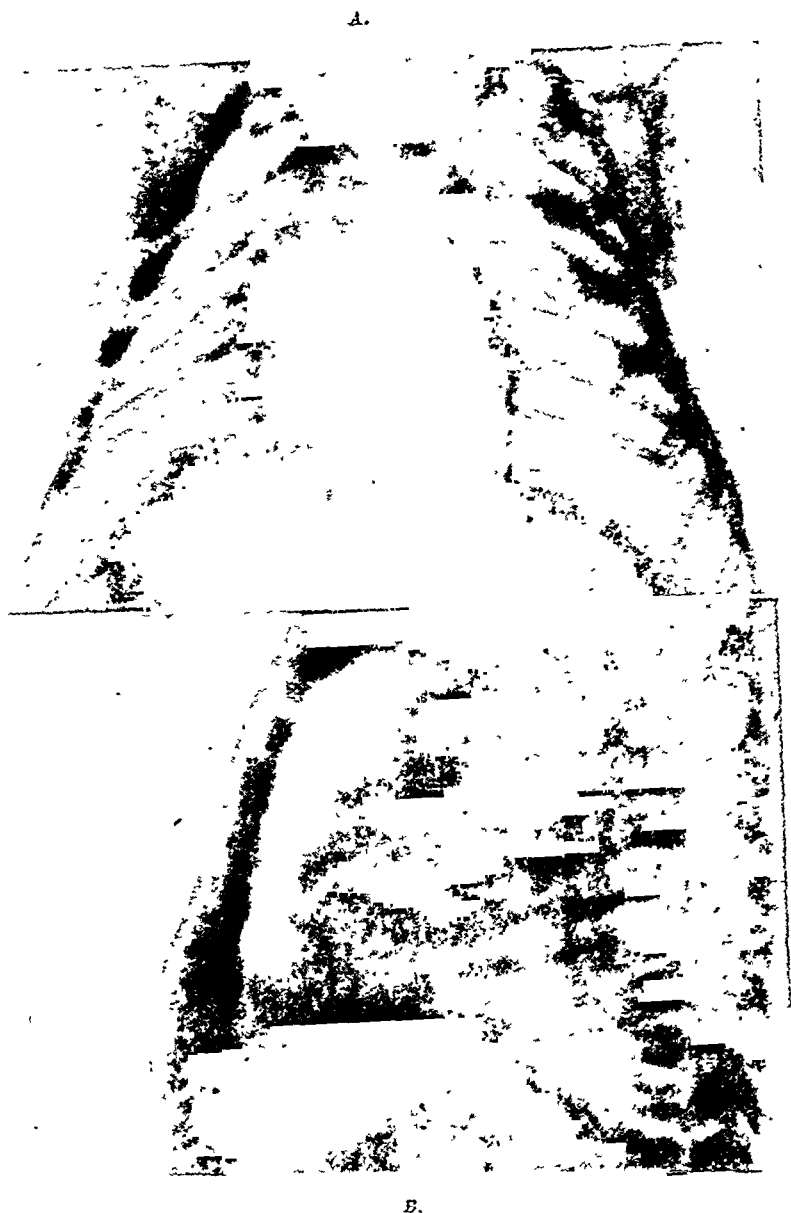
*Post-mortem examination.*—The pleural spaces were not entered under water. A left PT had previously been demonstrated by fluoroscopy. There was no ME. There was no gross PIE. The lungs were not subjected to fixation before cutting. All lobes of the lung were firm and dark red; they sank in water. On the posterior surface of the left lower lobe there were several perforations, probably needle punctures complicating the thoracenteses. The lungs were not examined with a dissecting microscope.

Sections for microscopic examination were made from two areas. The sites from which the blocks were taken are not known. Most of the bronchioles were moderately dilated. Some were ruptured, and several contained amniotic fluid debris. There was moderate to marked diffuse ectasia throughout the sections with small foci of compressed alveoli. The largest air spaces noted were adjacent to or communicating with bronchioles. The alveolar walls were congested and thickened; small hemorrhages were present. In some areas where the ectasia was most marked, the bronchioles were partially or completely collapsed. The interlobular septa were markedly widened, with either formation of elongated defects, frequently extending into the pleura, or with an extremely loose arrangement of the connective tissue fibers, forming wide interstitial spaces. Large ovoid spaces with a smooth lining contour were noted in the septa, usually occurring adjacent to blood vessels. A thin layer of fibrin was attached to the pleura.

The adrenals showed marked bilateral medullary hemorrhage. The remainder of the examination was essentially negative. There was neither cervical nor retroperitoneal emphysema. The brain was negative.

**CASE 3.**—Infant G., a boy, was born Aug. 18, 1945, at 10:12 P.M., at Hermann Hospital, weighing 2,700 Gm. Delivery was spontaneous of a 15-year-old white primipara. Position was left occipitoanterior. The mother was admitted in advanced labor but apparently the first two stages lasted about seven hours altogether. She delivered without anesthesia. She suffered a second degree laceration. The amniotic fluid contained a large amount of meconium and the infant's skin was covered with meconium. Although the infant's mouth and pharynx were full of mucus and meconium, respiration was prompt and spontaneous.

On August 19, at 9:00 A.M., the infant was noted to be cyanotic, and by 11:00 A.M. marked respiratory distress was evident. The chest was markedly expanded with minimal respiratory excursion. Expiration seemed difficult and incomplete. Resonance to percussion was questionably impaired over the right chest. Moist râles were heard in both bases,



B.

Fig. 2.—A, Case 3. AP view with the infant lying on his back. The reason for the marked shift of the heart and other mediastinal structures to the right is not apparent. Another AP view taken at the same time suggested emphysema of the left upper lobe or a large collection of air in the left upper mediastinum, or between the mediastinum and left upper lobe.

B. Lateral view with the infant lying on his right side. There is a large collection of substernal air, seemingly in the anterior and superior mediastinal spaces. Post-mortem examination showed bilateral PT and extensive bilateral PIE, but no MLE.

but were more marked on the right. Heart sounds could be heard better to the right of the sternum than to the left. Oxygen was started and inhalations of 5 per cent carbon dioxide and 95 per cent oxygen were ordered.

During the afternoon the infant did not improve and his temperature rose to 103° F., possibly because of undue heat from the incubator in which he was placed. At 2:00 P.M., and again at 6:00 P.M. he was given 50 c.c. of normal saline subcutaneously.

At 6:30 P.M., anteroposterior and right lateral roentgenograms of the chest were made. These films are illustrated in Fig. 2.

The infant continued to do poorly and at 9:00 P.M. an attempt was made to aspirate air from the anterior mediastinum; no air was obtained. A left thoracentesis, however, obtained 25 c.c. of air. A right thoracentesis was not performed. The infant expired at 9:35 P.M.

*Post-mortem examination.*—The pleural spaces were carefully entered under water and several bubbles of air escaped from each side. There was no ME. Numerous subpleural blebs of air were present on all surfaces of all lobes. These blebs were particularly marked in the hilar regions. A drawing of the thoracic viscera is illustrated in Fig. 3.

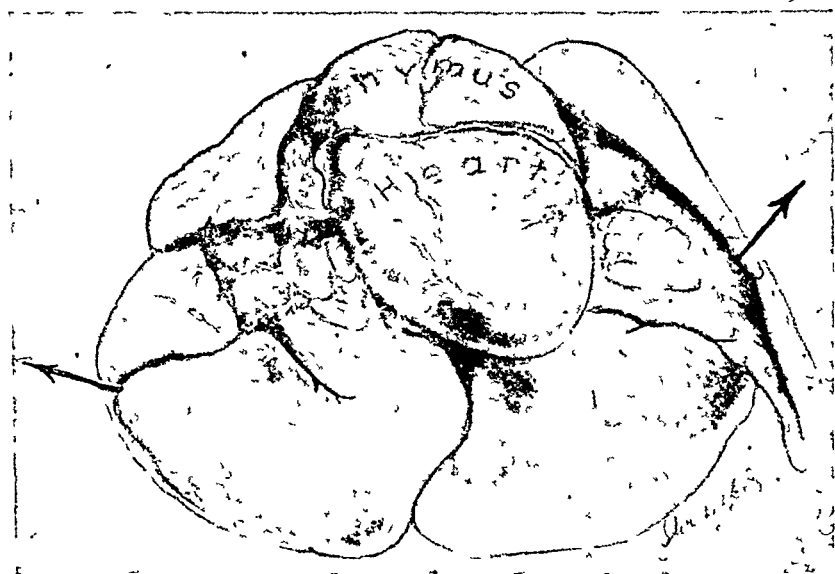


Fig. 3.—Case 3. A drawing of the thoracic viscera. Note the large subpleural blebs of air  
Note the absence of ME

After fixation of the lungs in 10 per cent formalin, they were cut and examined under a dissecting microscope. The same findings were present in all lobes; however, they were not so marked in the upper lobes. There was extensive perivascular interstitial emphysema. Extensive interstitial emphysema extended along connective tissue planes and along interlobular septa to the pleura. Some of the interstitial emphysema was in small pockets. All of these changes were particularly marked in the hilar regions. There was marked ectasia. Some idea as to the extent of these changes may be obtained from Figs. 4, 11, and 12.

A section from each lobe was taken for microscopic examination. Most of the bronchi and bronchioles were markedly dilated. Some were ruptured. Many of the bronchioles contained blood, and several contained meconium. Alveolar ectasia was marked.

Some of the lobules appeared cystic. Large defects were present in the septa and the pleura; in some of these blood was present. The defects communicated with alveoli. The perivascular spaces were exceptionally large.

Although the cranium was not entered, a cisternal puncture obtained grossly bloody fluid. The remainder of the examination was essentially negative. There was neither cervical nor retroperitoneal emphysema.

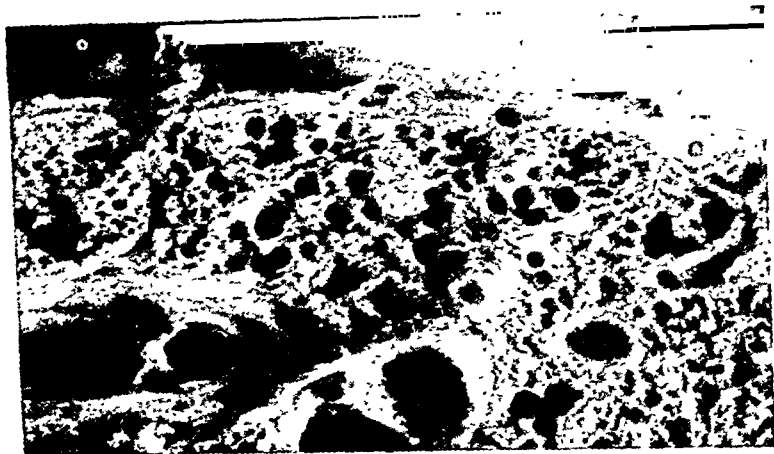


Fig. 4.—Case 3. Very low magnification (approximately  $\times 7$ ) of the cut surface of the fixed left lower lobe to show the marked ectasia. Some of these collections of air are in normal pathways and some are not.

CASE 4.—Infant G. L. S., a boy, was born Feb. 12, 1946, at 4:53 A.M., weighing 3,930 Gm. Delivery was spontaneous with episiotomy of a 23-year-old white primipara. Presentation was left occipitoanterior. The first two stages of labor lasted about four hours. The mother received 100 mg. of Demerol twice and 0.4 mg. of scopolamine once during labor. She received cyclopropane and oxygen during delivery. Respiration was prompt and spontaneous. The immediate neonatal period was uneventful. On February 13 a physical examination was negative, and the infant was discharged from the hospital.

On February 18, the infant became dyspneic and cyanotic. He was brought to the hospital emergency room. No diagnosis could be made and no treatment was instituted. The complaints subsided spontaneously.

On February 19, the infant developed diarrhea which was treated symptomatically and with subcutaneous fluids. On February 20 a physical examination was negative. On February 22 the infant again became dyspneic and cyanotic but only to a slight degree. The diarrhea continued.

On February 23, the infant was admitted to the Hermann Hospital. Physical examination showed moderate dehydration, slight cyanosis, and moderate dyspnea. The chest seemed to be hyperexpanded. The percussion note was hyperresonant over the entire chest. A blood count showed: hemoglobin, 20 Gm.; red blood cells, 5,400,000; white blood cells, 17,100; differential, a slight shift to the left. Urinalysis showed a heavy trace of albumin. Anteroposterior and left lateral roentgenograms of the chest were made. The anteroposterior view was negative; the left lateral view showed a small collection of substernal air. The infant was placed in a heat tent because his rectal temperature fell to 97.6° F. This may also possibly account for the temperature of 101° F. which he developed within the next twelve hours. The infant was given 250 c.c. of normal saline subcutaneously.

On February 24 at noon, the infant was critically ill and markedly dehydrated. The skin had a firm, almost hard texture. The infant was cyanotic and dyspneic. Respiration was

rapid but the excursion was shallow. The chest was markedly expanded, apparently kept at full inspiration, and the sternum and anterior part of the chest seemed to protrude forward. Intravenous fluids were begun and after the infant had received about 80 c.c., heart action ceased, although respiration continued. On efforts to administer intracardiac epinephrine, air was obtained on the first two attempts. Then it was realized that a left PT was present and that the heart was to be found on the right side of the sternum. Following intracardiac epinephrine, heart action resumed. Oxygen had been started in the meantime. On left thoracentesis it was found impossible to reduce the amount of air in the left pleural space: the PT was under considerable tension, and air apparently entered as rapidly as it could be aspirated. At 1:15 P.M. anteroposterior and right lateral roentgenograms of the chest were made. These films are illustrated in Fig. 5. At 1:25 P.M. the anterior mediastinal space was aspirated and 30 c.c. of air obtained; however, the operator could not be certain that he was not in the left pleural space. A right thoracentesis obtained no air. A left thoracentesis again showed that it was impossible to evacuate all of the air from the left pleural space. Subcutaneous fluids were administered.

During the afternoon the infant continued to do poorly, remaining cyanotic with rapid, shallow respiration and an expanded chest. Heart action was irregular. Another attempt to evacuate air from the left pleural space failed: air entered as rapidly as it could be aspirated. The tension PT forced air out into the subcutaneous tissues in the region of the thoracenteses. Intracardiac epinephrine was repeated. The infant expired at about 6:40 P.M.

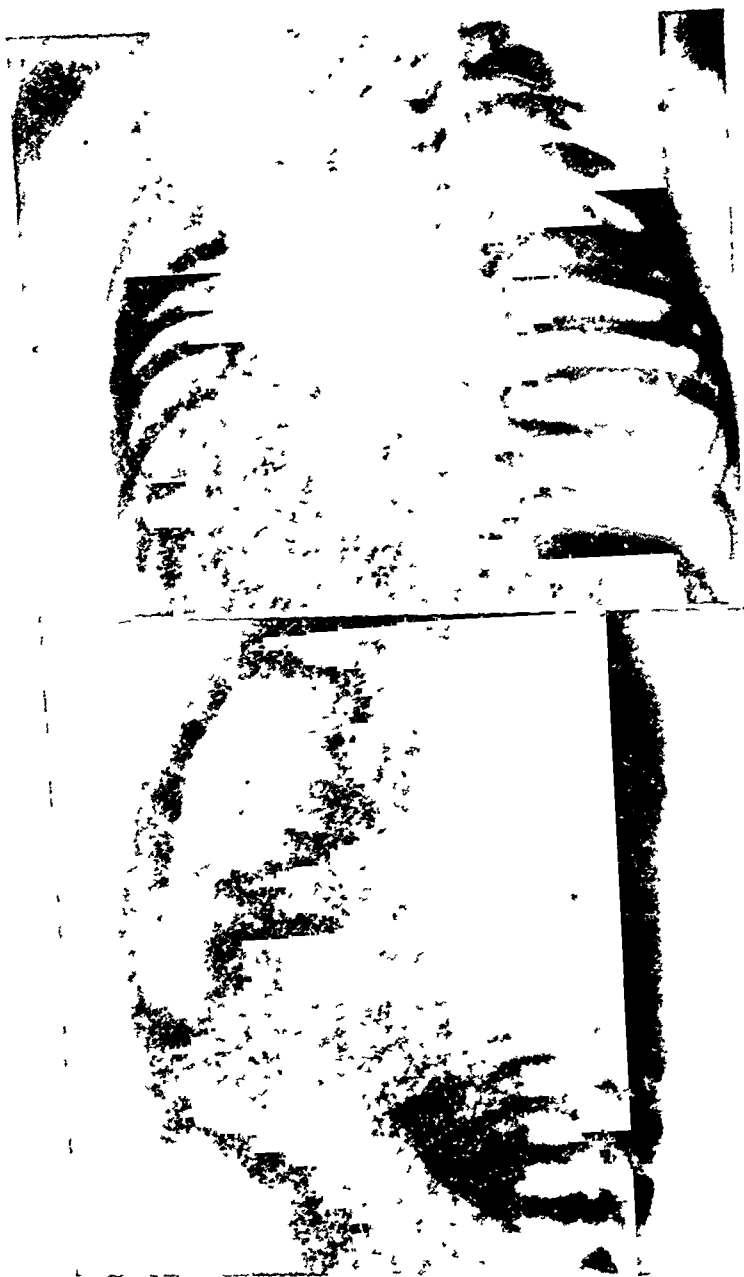
*Post-mortem examination.*—There was subcutaneous emphysema in the region of the left thoracenteses. The pleural spaces were carefully entered under water. A tension left PT and a small right PT were demonstrated. There was no ME. There was no gross PIE. The uncut lungs were not subjected to fixation. The lungs were not examined with a dissecting microscope. Sections for microscopic examination were made from two areas. The sites from which the blocks were taken are not known. In the sections examined, there was slight congestion and a few small areas of complete atelectasis. These sections were not available for subsequent review. The heart showed a patent ductus arteriosus. Microscopic examination of the ductus showed slight fibrosis and lymphocytic infiltration in the adventitia; the intima was replaced by almost acellular material in which lay a few fibroblasts. The remainder of the examination was essentially negative. There was neither cervical nor retroperitoneal emphysema. The brain was negative.

CASE 5.—Infant W., a boy, was born Feb. 20, 1946, at Hermann Hospital, at 2:09 A.M., weighing 3,500 Gm. Delivery was accomplished with low forceps without episiotomy. Position was left occipitoanterior. The mother was a 22-year-old Negro, gravida 3, para 2. The first two stages of labor lasted about ten hours. The mother received 100 mg. of demerol intramuscularly during labor and Pentothal Sodium intravenously during delivery. The infant was born with the umbilical cord around his neck. The skin was deeply stained with meconium. About two hours was required to establish respiration. A tracheal catheter, Coramine, oxygen, and artificial respiration (type not recorded) were all used. Finally the infant began to breathe in gasps.

The infant continued to do poorly. Oxygen was administered continuously. Respiration was rapid and shallow. At 11:00 A.M., physical examination showed marked molding of the head with overriding of the cranial bones. There was a hematoma of the right eye and scalp. The percussion note over the left chest was dull. At 2:00 P.M., anteroposterior and left lateral roentgenograms of the chest were made. These films are illustrated in Fig. 6.

At 2:45 P.M., the anterior mediastinal space was aspirated and 15 c.c. of air obtained. A left thoracentesis obtained 20 c.c. of air and a right thoracentesis obtained 8 c.c. of air. At 3:30 P.M., the roentgenographic examinations were repeated. These films are illustrated in Fig. 7. At 5:00 P.M., 180 c.c. of air was removed from the right pleural space. The infant expired at 5:45 P.M.

A.

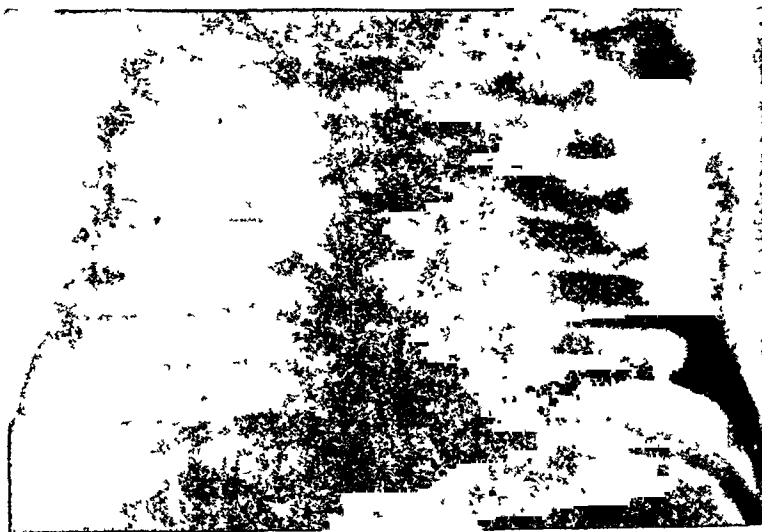


B.

Fig 5—A, Case 4 AP view with the infant lying on his back. There is atelectasis of the right upper lobe. There is a partial left PT. It is surprising that there is not a larger left PT and a more marked collapse of the left lung, because thoracenteses demonstrated that the air in the left pleural cavity was under great tension (note how the left diaphragm is forced downward). This suggests that the further collapse of the left lung was prevented by trapped air, likely PIE.

B, Lateral view with the infant lying on his right side. There is a large collection of substernal air, seemingly in the anterior and superior mediastinal spaces. Post-mortem examination showed a tension left PT and a small right PT. There was no ME.

A.



B.

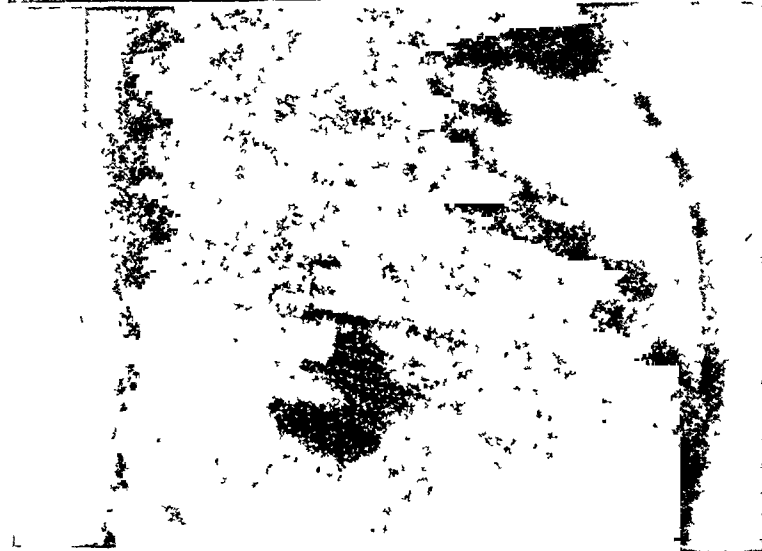


Fig 6—A, Case 5 at 2 00 P.M. AP view with the infant lying on his back. There is some atelectasis of the left upper lobe. There is marked emphysema of the right lung and probably of the left lower lobe.

B, at 2.00 P.M. Lateral view with the infant lying on his left side. There is a large collection of substernal air, seemingly in the anterior and superior mediastinal spaces



Fig. 7.—A, Case 5 at 3 30 P.M. AP view with the infant lying on his back. There is a partial left PT with a surprisingly marked shift of the heart and other mediastinal structures to the right for the small amount of left PT. At post-mortem examination the air in the left pleural space was found to be under very high tension. There was also extensive bilateral PIE which, in the case of the right lung, probably prevented any further shift of the heart and other mediastinal structures and which, in the case of the left lung, probably prevented any further collapse.

B, at 3 30 P.M. Lateral view with the infant lying on his left side. There is no sub-sternal collection of air to suggest air in the anterior mediastinal space. Post-mortem examination, however, showed extensive ME.



*Post-mortem examination.*—The pleural spaces were carefully entered under water. A tension left PT was demonstrated. On the right a considerable quantity of air also escaped, about one-fourth as much as on the left. There was extensive ME. Numerous subpleural blebs of air were present on all surfaces of all lobes. These blebs were particularly marked in the hilar regions. A drawing of the thoracic viscera is illustrated in Fig. 8. The entire lungs were fixed in 10 per cent formalin before cutting. The lungs were not examined with a dissecting microscope.



Fig. 8.—Case 5. A drawing of the thoracic viscera. Note the large subpleural blebs of air. Note the extensive ME.

A section from each lobe was taken for microscopic examination. There was moderate dilatation and occasional rupture of the smaller bronchioles. The bronchioles and alveoli contained meconium and amniotic fluid debris. Alveolar ectasia was moderate in the right lung and slight in the left lung. Some of the defects in the septa and pleura of the right lung were so large that they were termed bullous. Perivascular emphysema was slight when compared to that found in the other patients. Congestion was equally marked in the large arteries and veins. Some of these changes are seen in Fig. 9.

The remainder of the examination was essentially negative. There was neither cervical nor retroperitoneal emphysema. The brain was negative.

**CASE 6.**—Infant S., a girl, was born July 10, 1946, at Hermann Hospital, at 5:30 p.m., weighing 3,260 Gm. Delivery was accomplished with low forceps without episiotomy. Position was left occipitoposterior, spontaneously rotating to left occipitoanterior. The mother was a 22-year-old Negro, gravida 5, para 4. She was admitted in advanced labor, but apparently the first two stages lasted about eleven hours altogether. The mother received Pentothal Sodium intravenously during delivery. The infant was born with the umbilical cord wrapped once around her neck. The amniotic fluid was stained with meconium and the infant's mouth and nose were full of meconium. Respiratory efforts were poor but included the use of the accessory muscles of respiration. Efforts at resuscitation included the use of a tracheal catheter, coramine, inhalations of oxygen, and a mechanical respirator.

The infant became cyanotic in spite of the continuous administration of oxygen. Respiration was labored and the chest was hyperexpanded. At first no breath sounds could be heard over the entire chest; later they could be heard accompanied by fine crackling râles. There was a large cephalohematoma.

The infant grew worse. Although the entire body was cyanotic, the cyanosis was much worse about the head and neck. The chest became markedly expanded, being maintained at extreme inspiration, with a small respiratory excursion. At 11:30 P.M. anteroposterior and left lateral roentgenograms of the chest were made. These films are illustrated in Fig. 10. At 11:45 P.M. the infant expired.

*Post-mortem examination.*—The pleural spaces were carefully entered under water. A large amount of air escaped from the right pleural sac so rapidly as to suggest that it had been under considerable tension. No air escaped from the left, however. There was no ME. Numerous subpleural blebs of air were present on all surfaces of the right lower, right middle, and left lower lobes.

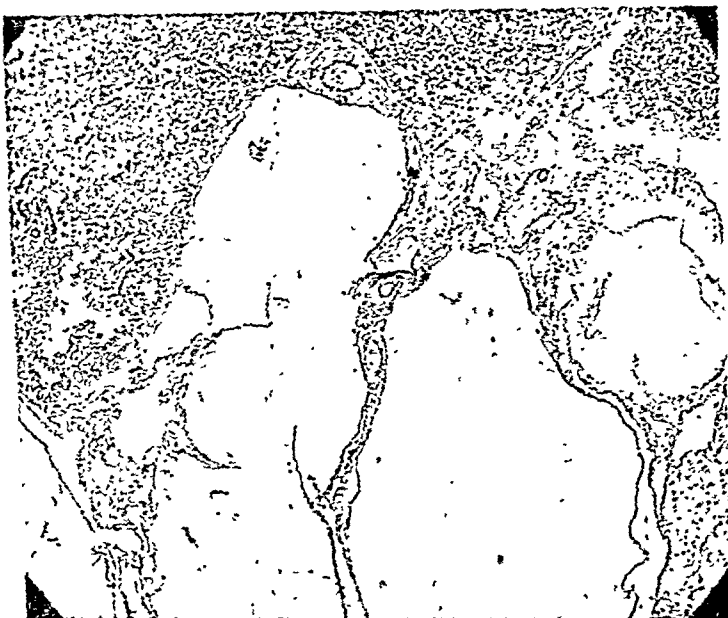


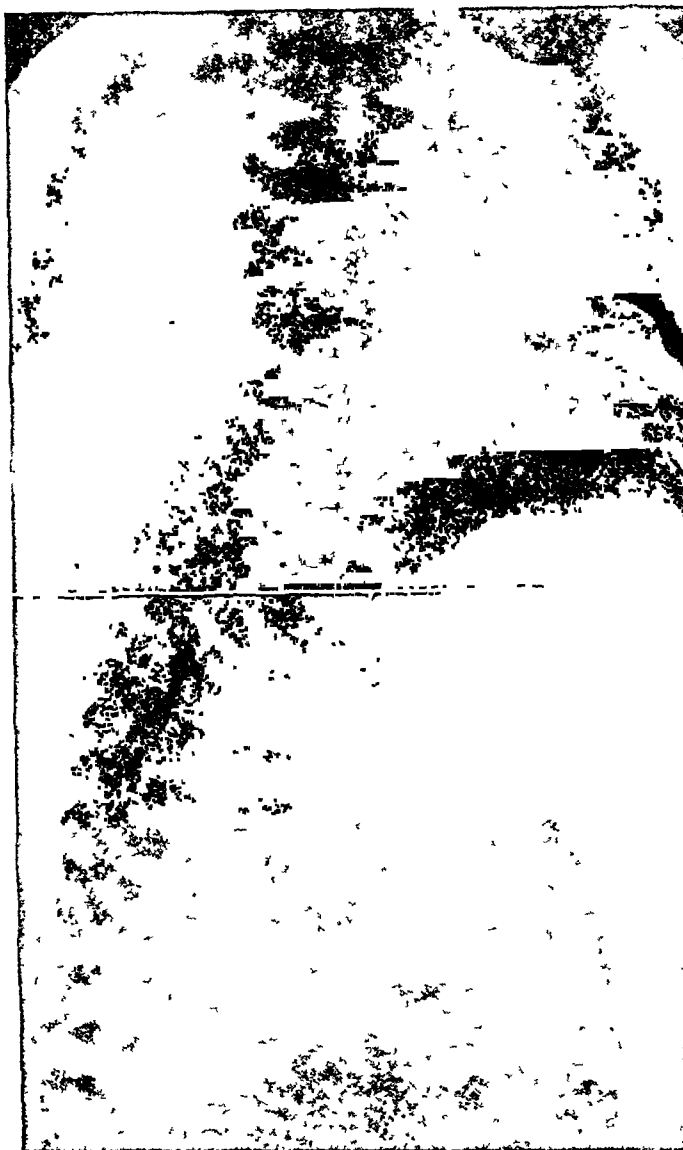
Fig. 9.—Case 5. Photomicrograph (approximately  $\times 75$ ) of a section from the right middle lobe. Note the dilated and torn alveoli, the hemorrhage, and the adjacent atelectatic area.

After fixation of the lungs in 10 per cent formalin, they were cut and examined under a dissecting microscope. The same findings were present in all lobes. There was extensive perivascular interstitial emphysema. Extensive interstitial emphysema extended along connective tissue planes and along interlobular septa to the pleura. Some of the interstitial emphysema was in small pockets. All of these changes were particularly marked in the hilar regions. There was marked ectasia. Some idea as to the extent of these changes may be obtained from Figs. 4, 11, and 12.

Sections were taken from each lobe for microscopic examination. Alveolar ectasia was marked. There was marked septal, pleural, and perivascular interstitial emphysema with apparent communications with alveoli. Hemorrhage into the spaces was marked. Some of these changes are seen in Figs. 13 and 14.

The heart showed a few small epicardial petechiae. The remainder of the examination was essentially negative. There was neither cervical nor retroperitoneal emphysema. The brain was negative.

A.



B.

FIG. 10—A, Case 6. AP view with the infant lying on her back. There is atelectasis of almost the entire left lung except the lower portion of the left lower lobe. There is a partial right PT. It is surprising that there is not a larger right PT and a more marked collapse of the right lung, because autopsy demonstrated the PT to be a tension one. This suggests that the further collapse of the right lung was prevented by trapped air, likely PIE. Note that the air in the right pleural space seems to extend across the midline to the left of the vertebral column. This probably explains the substernal collection of air seen in the left lateral view (See FIG. 10B).

B, Lateral view with the infant lying on her left side. There is a collection of substernal air seemingly in the anterior mediastinal space. This, however, is probably air in the right pleural sac herniating across the midline in the anterior mediastinal space (See FIG. 10, A). Post-mortem examination showed a right tension PT and bilateral PIE, but no ME.

## PATHOLOGY

The most revealing investigation of the pathogenesis and problem of air outside of the normal respiratory pathways has been that of Macklin. A review of both experimental and clinical aspects of which he is a co-author<sup>3</sup> should be studied by anyone interested in this subject. His work<sup>8</sup> demonstrates that the most likely and probably the most common sequence of events is as follows: air first passes through multiple and minute ruptures of the alveolar walls which border upon blood vessels, to form perivascular collections of air. From here the air progresses along the blood vessels to reach the mediastinum. From the mediastinum the air may travel superiorly to produce cervical subcutaneous emphysema, or travel inferiorly to produce retroperitoneal emphysema and pneumoperitoneum. Also from the mediastinum the air may travel into the interstitial tissue of the other lung, rupture into the pericardial sac, or rupture the mediastinal pleura to enter the pleural sac.



FIG. 11.—Case 6. Very low magnification (approximately  $\times 55$ ) of the cut surface of the fixed right lower lobe. A, Large collection of air dissecting along the interlobular septum to the visceral pleura. B, Large subpleural blebs. The visceral pleura was torn away along the superior interrupted line to form a subpleural bleb of air and split along the inferior interrupted line to form a bleb of air in the pleura. C, Semicircular collection of air about a blood vessel. D, Collections of air outside of the normal pathways. Other similar collections may be seen. Note the generalized ectasia.

All except one (Case 4) of the patients reported here had PIE, and in this exception the lungs were not fixed before cutting, the lungs were not examined with a dissecting microscope, and the stained sections were not available for subsequent review. Only one (Case 5) had ME. None had cervical subcutaneous emphysema. None had retroperitoneal emphysema. However, all six

patients had PT. The obvious implication is that, in the newborn infant, interstitial pulmonary air *can* rupture the visceral pleura to produce PT directly. This is apparently what happened to two of three rabbits when Macklin<sup>8</sup> subjected their lungs to general overinflation. Van Allen and associates<sup>9</sup> had a similar experience with the lungs of rabbits. This suggests that the structure of the lungs in the newborn infant more closely approximates that of the rabbit than that of various other animals used by both investigators. This does not mean that in the newborn infant the air may not enter the mediastinum. Certainly it did in Case 5. Fisher<sup>10</sup> has reported a newborn infant

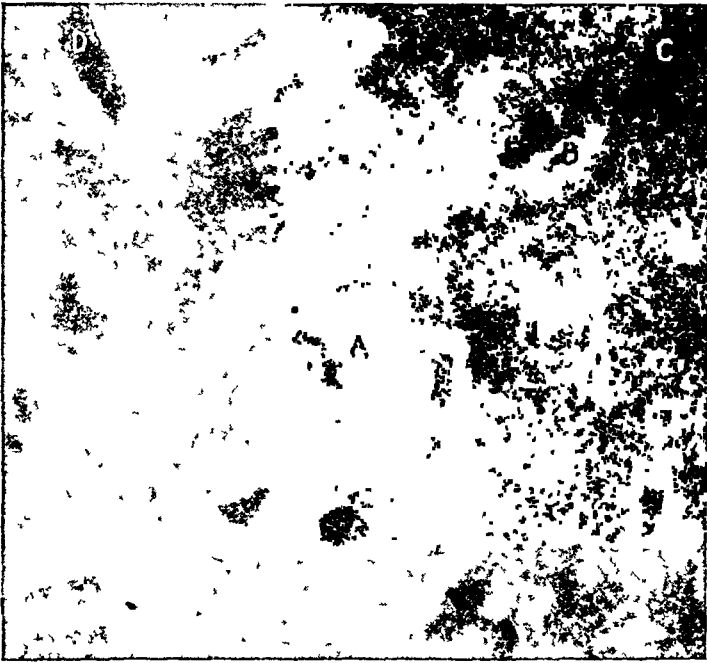


Fig. 12—Case 6 Very low magnification (approximately  $\times 7$ ) of the cut surface of the fixed right middle lobe. *A*, Perivascular collection of air which extends along an interlobular septum to surround a second vessel at *B* and continues beyond *C* to reach the pleura just outside the field. *D*, Collection of air outside of the normal pathways.

coming to autopsy who had PIE and ME but not PT. Nor does it mean that in the newborn infant ME may not precede PT so as to suggest that the first caused the second. Gumbiner and Cutler<sup>11</sup> mentioned such a case. It seems very likely that in newborn infants interstitial pulmonary air can produce PT by either of two mechanisms: (a) rupturing the visceral pleura directly, or (b) first producing ME and then rupturing the mediastinal pleura.

Joannides and Tsoulos<sup>6</sup> found that dogs, in whose pleural cavities a small rubber catheter had been introduced to allow the escape of air, survived an intratracheal blast of air fatal to other dogs not so treated. This emphasizes the importance of PT in airblock. However, in the newborn infant, PIE and ME may prove fatal without PT intervening.<sup>10</sup> Moreover, in the newborn

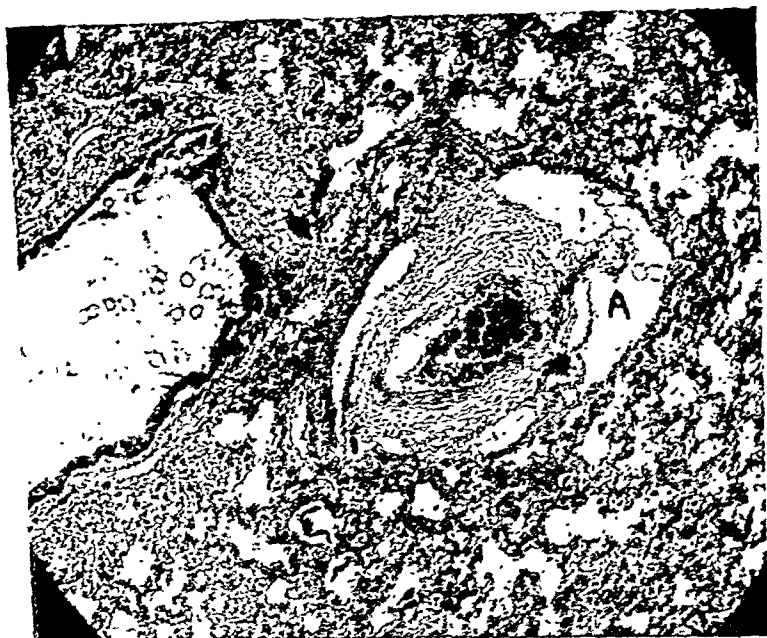


Fig. 13.—Case 6. Photomicrograph (approximately X75) of a section from the left lower lobe. A, Perivascular collection of air with hemorrhage into the space thus produced. Note the thickened torn walls of the alveoli

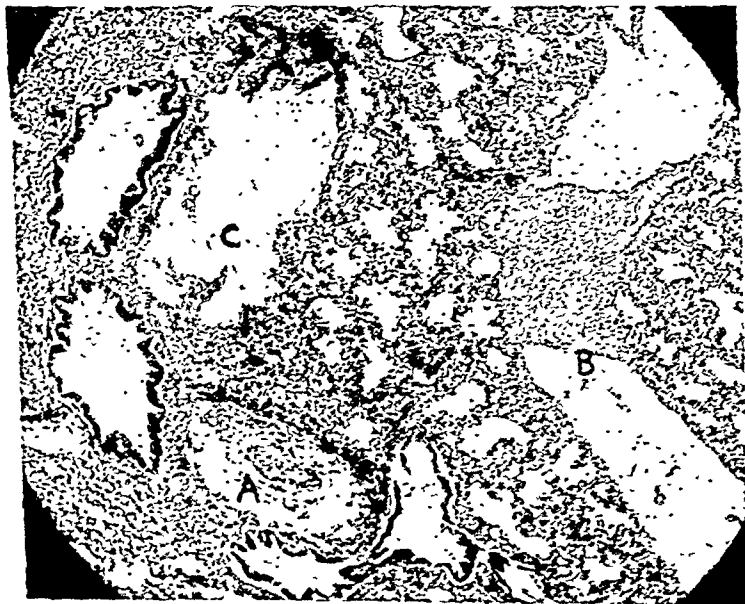


Fig. 14.—Case 6. Photomicrograph (approximately X75) of a section from the left lower lobe. A, Perivascular collection of air with hemorrhage into the space thus produced. B, linear space, and C, oval space produced by air outside of the normal pathways. In each instance note the hemorrhage.

infant ME has been observed which showed evidence of reduction of the ME and clinical improvement coincident with the development of PT.<sup>11</sup> These views may be partially reconciled by the fact that pneumothoraces may vary in amount, in tension, and in whether unilateral or bilateral. Four (Cases 2, 4, 5, and 6) of our six patients indicate that in the presence of PIE an apparently small or moderate PT may be under a very high tension. The air trapped in the lung tissue prevents more than a moderate collapse. It has been stressed<sup>3</sup> that the pressure in a PT can be raised to greater than atmospheric only by expiration and not by inspiration. It is only during expiration that air in the lung is under a pressure greater than atmospheric, and may be under a pressure much greater than atmospheric during forced expiration. It may be easily understood that air trapped in the lung tissue, tending to splint it in an expanded form, might lead to strong expiratory effort.

In animals, ME alone may result in grave consequences, probably because of pressure on the great vessels.<sup>12, 13</sup> In newborn infants, aspiration of ME may relieve alarming symptoms.<sup>11</sup>

To our knowledge there is no report of an autopsy on a newborn infant in which the sole finding that could have caused the death was PIE. Nevertheless, at autopsy we have been deeply impressed with this finding, particularly when it is widespread. Being trapped in the lung, the air holds it in a state of inflation and splints it so as to prevent deflation. In some of our patients PIE was so extensive that it was difficult to understand how there could have been a significant respiratory excursion. This, together with the interference in the pulmonary circulation occasioned by compression of the vessels by the perivascular collections of air, might easily be fatal.

Certainly the possibility of PIE leading to air embolism (as already discussed) needs further investigation. Lindblom<sup>14</sup> found air in the circulatory system of newborn infants who failed to respond to strenuously applied methods of artificial respiration.

Apparently, extension of the air to extrathoracic locations is not a serious complication. Its appearance in the cervical subcutaneous tissues may be accompanied by clinical improvement, the pressure caused by the aberrant air inside the chest having been decreased.<sup>3</sup> Cervical subcutaneous emphysema,<sup>7, 15, 16</sup> retroperitoneal emphysema,<sup>17</sup> and pneumoperitoneum<sup>7</sup> have been reported complicating airblock in the newborn period.

One very interesting aspect of airblock is the probability of acute or, possibly better, subacute cor pulmonale. Pulmonary hypertension resulting from pressure on the pulmonary vessels by perivascular collections of air very likely increases considerably the work of the right ventricle. Some evidence of this, such as dilatation of the right ventricle, might be present at autopsy. We are not able to discuss this phase of the subject further, since these patients were not examined with this particularly in mind. However, evidence very indicative of pulmonary hypertension is mentioned later in a footnote under the discussion of etiology.

## ETIOLOGY

As PIE is apparently the first and essential step in the production of airblock, a search for the cause narrows to this phase. Macklin's work<sup>8</sup> indicates: (a) that PIE may occur when alveoli are overinflated, particularly when accompanied by increased intra-alveolar pressure; and (b) that PIE may occur when the caliber of the pulmonary blood vessels is reduced, particularly when accompanied by increased intra-alveolar pressure. The caliber of the pulmonary blood vessels may be reduced by heart failure, stenosis or insufficiency of the pulmonary valve, or pulmonary embolism. However, it has been emphasized<sup>8</sup> that forced expiration will result in a decreased return of blood to the right heart and therefore a reduced amount of blood available for the pulmonary circulation. This will result in a correspondingly decreased caliber of the pulmonary blood vessels.

PIE, then, might result from compensatory overinflation occasioned by atelectasis. Four (Cases 1, 4, 5, 6) of our six patients had roentgenographic evidence of atelectasis. PIE might more easily be produced in the presence of congenital heart disease. Of sixty-nine patients with PT in the newborn period reviewed by DeCosta,<sup>7</sup> four had cardiac anomalies. One (Case 4) of our six patients had a patent ductus arteriosus. However, it is doubtful if much importance can be attached to this particular anomaly at this stage of life.\* PIE might result from the irregular respiration sometimes caused by intracranial hemorrhage. Of three autopsied newborn infants with PT reported by Elkin,<sup>17</sup> all had intracranial hemorrhage. In four of our six patients the brain was negative. In two it was not examined; however, one of these two (Case 3) had bloody cisternal fluid.

In three (Cases 3, 5, and 6) of our six patients the amniotic fluid was stained with meconium. This is commonly taken as evidence of fetal distress, particularly anoxia. In two (Cases 3 and 5) microscopic sections of the lung showed meconium in the bronchioles. In one (Case 2) version and extraction was necessitated by prolapse of the umbilical cord. In two (Cases 5 and 6) the umbilical cord was wrapped around the infant's neck. Although one (Case 2) received two intracardiac injections of epinephrine before airblock was diagnosed, this does not necessarily indicate that the intrathoracic punctures led to the development of airblock. The condition of the infant was very poor, probably due to airblock, before the injections were administered. Moreover, in no other significant feature does this case differ from the other five. In four (Cases 1, 2, 5, and 6) it was very difficult to establish respiration. Two (Cases 1 and 5) received artificial respiration, but the type was not recorded. One (Case 6) received artificial respiration by means of a mechanical respirator. In four (Cases 1, 2, 5, and 6) efforts at resuscitation included the use of a tracheal catheter. In one (Case 4) the sequence of events suggests

\*In this case the microscopic appearance of the ductus arteriosus indicated to the pathologist, who performed the autopsy, that it had once closed and reopened. This reopening might have been due to pulmonary hypertension resulting from pressure on the pulmonary vessels by perivascular collections of air. This suggests that in this particular case the PIE was the cause of the ductus being open and not vice versa.



that airblock of mild to moderate severity was made much worse by hyperpnea occasioned by diarrheal acidosis.

It seems apparent that the factors related to the production of airblock experimentally<sup>3</sup> were easily present in these six patients.

Wilson and Farber<sup>18</sup> have shown that the expansion of airless lungs requires a much greater negative pressure than does normal inspiration. This was attributed to cohesion of the moist surfaces of the air passages in collapsed lungs. They concluded: "The first breath of a newborn baby may thus be its most difficult one. For a variable period after birth, especially vigorous inspirations must be maintained . . ." Striking changes in both the cells lining the alveoli and the connective tissue of the lung parenchyma are occasioned by the establishing of respiration. When these factors are considered, one wonders that PIE is not more frequent than is commonly believed; probably it is.

#### SYMPTOMS AND SIGNS

We do not think that a review of our patients adds any significant information to the symptomatology of airblock. This has been adequately outlined and discussed elsewhere.<sup>2, 7, 11, 17, 19</sup> For these reasons we are omitting a discussion of this aspect of the subject. We would, however, like to emphasize the striking appearance of some of these infants. The chest is expanded at or near full inspiration. In spite of effort, the infant is unable to more than partly expire. The respiratory excursion is therefore limited. This, together with cyanosis, should immediately suggest airblock.

#### ROENTGENOGRAPHIC FINDINGS

The criteria for a roentgenographic diagnosis of PT are quite well known and need no review here. As already mentioned, in the presence of PIE, the size of a PT may have no relationship to its pressure. The lung, splinted by the PIE, may be prevented from more than a moderate collapse; yet the PT may be under a very high tension, as evidenced by shift of the mediastinum and depression of the diaphragm.

The criteria for a roentgenographic diagnosis of pulmonary emphysema are also quite well known and need no review here. The differentiation of types of pulmonary emphysema may be difficult. As discussed by Caffey,<sup>20</sup> some information may be obtained by comparing inspiratory and expiratory findings: In compensatory emphysema, the heart and other mediastinal structures are pushed away from the involved lung on inspiration. In obstructive emphysema, the heart and other mediastinal structures are pushed toward the involved lung on inspiration, because of expansion of the other lung. In bilateral obstructive emphysema the cardiac and supracardiac shadows become smaller on expiration, because of the squeezing effect of the dilated lungs. This is contrary to what is normally seen.<sup>20</sup> Although in a comparison of inspiratory and expiratory findings PIE would no doubt act like obstructive emphysema, we did not include this procedure in our examination of these cases.

ME may be apparent on an anteroposterior or posteroanterior film\* of the chest as evidenced by a linear shadow of air along either side of the mediastinum or along the border of the heart. However, in the newborn infant, ME may be present yet these views not show it. For this reason the value of a lateral film of the chest has been stressed,<sup>11</sup> particularly for air in the anterior portion of the mediastinum. In this view the air is visible in a collection just posterior to the sternum. In a previous report<sup>2</sup> we have expressed our doubts as to the value of this view, if a PT is also present. We believe that we now have evidence to support these doubts.

In the five patients (Cases 1, 3, 4, 5, and 6) who had lateral roentgenograms, all showed a substernal collection of air. Yet only one (Case 5) had ME. All five had PT. The obvious implication is that PT can cause an apparent substernal collection of air. A valid criticism may be that the infants were photographed lying on the side and that this apparent substernal air is due to shift of air inside the pleural space. However, this criticism would not be important if the PT were under considerable tension, as was present in four (Cases 2, 4, 5, and 6) of the five patients. A tension PT would hold its form because of its pressure. Our conclusion is that PT alone, particularly if under tension, can cause an apparent collection of substernal air, probably because of herniation of the anterior mediastinum. Actually, a review of the figures illustrating the roentgenograms of Cases 1, 3, and 5 suggests that the expanded lung of PIE can cause an apparent collection of substernal air (this would be particularly true if the film were slightly overexposed).

Moreover, the one patient (Case 5) who did have ME showed an apparent collection of substernal air at 2:00 P.M. but not at 3:30 P.M. This may be due to the fact that 15 c.c. of air was aspirated from the anterior mediastinum at 2:45 P.M. From the loculated type of ME seen at autopsy (see Fig. 8) it is difficult to believe that the aspiration removed a high proportion of the air. The obvious implication is that extensive ME can be present although a lateral roentgenogram of the chest does not show a substernal collection of air.

#### TREATMENT

It is probable that most cases of airblock in newborn infants are slight and cause no symptoms. In many more the symptoms are mild and spontaneous recovery will likely ensue. Treatment of such patients may well be restricted to increasing the oxygen concentration of inspired air.

In patients with airblock of more than moderate severity, more vigorous therapeutic measures may be indicated. If a large PT or a tension PT is present, aspiration is advisable. If a tension PT recurs it may be desirable to perform a closed thoracotomy and connect the tube to a water trap so as to allow air to escape but not enter. This was done in Case 2. The advisability of this procedure is suggested by animal experiments.<sup>6</sup> Air may be

\*In newborn infants, it has been customary on radiology services with which the authors are familiar for anteroposterior views to be taken with the infant lying on the back. Lateral views are similarly taken with the infant lying on the side.

present in the mediastinum in an amount sufficient to warrant efforts at its removal. Surgical measures designed to relieve ME have been reviewed by Hammond.<sup>21</sup> Since aspiration of the anterior mediastinum may remove a significant amount of air,<sup>11, 19</sup> this step should be tried first. A therapeutic approach to the problem of PIE is more difficult. Removal of air from extensions such as ME or PT might relieve the pressure of the PIE.

### CONCLUSIONS

1. Methods of post-mortem examination used in the newborn period should include measures to detect the presence of aberrant air.

2. In newborn infants, interstitial pulmonary air can produce pneumothorax by either of two mechanisms: (a) rupturing the visceral pleural directly, or (b) first producing mediastinal emphysema and then rupturing the mediastinal pleura.

3. The possibility of pulmonary interstitial emphysema producing air embolism needs further investigation.

4. The effect of pulmonary interstitial emphysema upon the heart needs further investigation.

5. Factors which may lead to the production of pulmonary interstitial emphysema are not infrequently present in the newborn period. The incidence of pulmonary interstitial emphysema in this period is undoubtedly higher than is commonly believed.

6. In the presence of pulmonary interstitial emphysema, the size of a pneumothorax may have no relationship to its pressure. The lung, splinted by the pulmonary interstitial emphysema, may be prevented from more than a moderate collapse, yet the pneumothorax be under a very high tension.

7. An apparent substernal collection of air in a lateral roentgenogram of the chest is not diagnostic of mediastinal emphysema, if a pneumothorax is also present. Moreover, mediastinal emphysema of significant proportions may exist without this roentgenographic sign being present.

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# SULFADIAZINE PROPHYLAXIS IN CHILDREN AND ADOLESCENTS WITH INACTIVE RHEUMATIC FEVER

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THE use of sulfanilamide as a prophylactic agent against recurrences of active rheumatic fever in patients with inactive rheumatic fever has been reported by various observers.<sup>1-10</sup> The combined evidence of these articles pointed to a significantly lower rate of recurrence among the treated cases. In some series,<sup>4, 8</sup> however, the occurrence of various toxic manifestations from sulfanilamide constituted a considerable problem. With the advent of sulfadiazine, and encouraged by the favorable results in our four years' experience with sulfanilamide prophylaxis, it seemed advisable to make further observations using sulfadiazine daily as a prophylactic agent in inactive rheumatic fever. Not only was sulfadiazine known to be as effective against Beta hemolytic streptococci as sulfanilamide, but it also had the added advantages of a lower incidence of toxic manifestations and a somewhat more prolonged maintenance of drug concentration in the blood.

The present report deals with two years' experience with sulfadiazine given prophylactically to a group of inactive rheumatic subjects regularly under the care of the Bellevue Children's and Adolescents' Cardiac Clinics. The study was made from October, 1943, to October, 1945. Due to wartime curtailment in medical and laboratory staff, the group was of necessity smaller than one would have wished, the total number of patients having been curtailed to allow for closer individual supervision.

## TREATED AND CONTROL GROUPS

*Selection of Cases.*—Two groups of equal size were selected for this study, one to receive prophylactic treatment, the other to serve as controls. All patients had a definitely established rheumatic past history, but were in the inactive stage both by clinical and laboratory criteria when admitted to the study groups. Each patient to receive sulfadiazine was matched as closely as possible with an individual control patient in respect to sex, age, years since last signs or symptoms of rheumatic activity, number and severity of previous rheumatic attacks, and degree of cardiac involvement.\*

The length of previous prophylaxis was also matched in those control and sulfadiazine-treatment patients selected from the group that had received sulfanilamide prophylactically in earlier years.

*Number of Patients and Length of Observation.*—There were fifty-one individuals each in the treated and control groups; in both groups, twenty-eight patients had received sulfanilamide previously, while twenty-three were new to

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\*Comparison of the treated and control groups in terms of the above factors is shown in Table I.

prophylactic treatment. Thirty-six subjects were treated throughout two years and fifteen through one year, the individual control patients being followed during concomitant years. Thus there were eighty-seven treated-patient years and eighty-seven control-patient years observed during the study.

*Clinic Procedure.*—Before admission to the treatment or control group, all patients were closely questioned and given a complete physical examination, and laboratory studies were made (erythrocyte sedimentation rate, electrocardiogram, and x-ray of the heart for size and shape) to serve as base line and to rule out rheumatic activity. No patient received the drug or was used as a control until three months or more after all evidence of previous rheumatic activity had ceased.

TABLE I. COMPARISON OF TREATED AND CONTROL GROUPS

COMPARISON FACTORS	TREATED GROUP (87 PATIENT YEARS) (%)	CONTROL GROUP (87 PATIENT YEARS) (%)
<i>Sex</i>		
Male	45	42
Female	55	58
<i>Age Distribution in years</i>		
4-8	6	6
9-12	17	15
13-16	54	51
17-21	23	28
<i>Years Since Last Rheumatic Attack</i>		
1	26	23
2	23	22
3	26	28
4	18	20
5	7	7
<i>Number of Previous Attacks</i>		
1	18	18
2	23	42
3	25	19
4	23	11
5	11	10
<i>Distribution of Cardiac Diagnoses*</i>		
Possible and Potential Heart Disease	26	29
Enlarged heart		
Mitral insufficiency	22	18
Mitral insufficiency and stenosis	30	28
Mitral insufficiency and stenosis and aortic insufficiency	15	18
Mitral insufficiency and stenosis and aortic insufficiency and stenosis	7	7

\*Diagnoses were made according to the criteria for the Classification and Diagnosis of Heart Disease: Heart Committee of the New York Tuberculosis and Health Association.

Patients in the treated group were examined, hemoglobin was determined and total white cell and differential counts and urinalysis were made once a week during the first seven weeks of sulfadiazine therapy. Subsequently, these patients were seen once a month for two months and at six-week intervals thereafter. Routine blood counts and urinalyses were not done at each visit beyond the eleventh week of treatment. These were checked, however, approximately every three months in patients showing no abnormal laboratory findings. In the few subjects where suspicious blood or urine changes occurred, the patient returned at frequent intervals for further laboratory studies.

The control patients were examined routinely every two to three months and more frequently where rheumatic activity was suspected. In both control and treated groups, sedimentation rates and electrocardiograms were taken repeatedly whenever there were symptoms or clinical signs suggestive of rheumatic recurrence.

*Drug Administration.*—Children weighing less than 110 pounds received a daily single dose of 0.5 Gm. sulfadiazine in the morning. Those weighing over 110 pounds took a daily total of 1 Gm. of sulfadiazine, one 0.5 Gm. dose in the morning and one at bedtime. The 4-year-old child (weight 33 pounds) maintained a satisfactory level on 0.25 Gm. once a day. With these doses, blood sulfadiazine levels were found to average between 1.0 and 3.5 mg. per cent. The drug was administered continuously throughout the year.

### *Rheumatic Recurrences.*—

*Treated Group:* One case of recurrent active rheumatic fever occurred during the eighty-seven patient years in the treated group.

L. B., a 14-year-old girl, whose rheumatic history started at the age of 6 years, had, by 9 years of age, developed a markedly enlarged heart and evidence of congestive failure sufficient to require digitalization. From the age of 10 years she received prophylactic sulfonamide during four seasons, getting along fairly well on restricted physical activity. In October, 1944, she developed pain in the chest and fever. She was found to have pericarditis and further evidence of congestive failure, gaining 5 pounds in one week. The liver was enlarged to four fingerbreadths below the costal margin. On absolute bed rest in the hospital and moderate doses of salicylates, the rheumatic activity and failure gradually receded. Despite repeated nose and throat cultures, no B hemolytic streptococci were found. However, there was a slight rise in the antistreptolysin titer of the blood.

*Control Group:* There were seven cases (six definite, one probable) of recurrent, active rheumatic fever in the eighty-seven patient years in the control group. The six definite cases included unequivocal signs of activity, both by clinical and laboratory evidence (Table II).

TABLE II. EVIDENCE OF RHEUMATIC ACTIVITY IN CONTROL CASES

CASE AGE (YR.)	CARDIAC DIAGNOSIS	FEVER	ARTHRITIS	TACHYCARDIA	DEVELOPMENT OF NEW MURMUR	ELEVATED SEDIMENTATION RATE	PRO-LONGATION OF P-R INTERVAL	INCREASE IN SIZE OF HEART BY X-RAY
W. K. 9	Possible and Potential	+	+	+	-	+	-	+
R. C. 13	Possible and Potential	-	+	-	+	-	-	+
J. P. 14	Possible and Potential	+	+	+	+	+	+	+
E. C. 14	EH MI MS AI	+	+	+	-	+	+	-
P. C. 17	EH MI MS AI	+	+	+	-	+	-	+
A. D. 17	EH MI MS AI AS	+	+	+	-	+	+	+

EH = enlarged heart; MI = mitral insufficiency; MS = mitral stenosis; AI = aortic insufficiency; AS = aortic stenosis.

The one control patient considered as probably active was a 20-year-old girl with an early onset of rheumatic history and advanced heart disease. She had received prophylactic sulfanilamide for three seasons until July, 1942. After that date without sulfa-prophylaxis there was no evidence of rheumatic activity until November, 1944. She then developed precordial pain, auricular fibrillation, and rapidly progressive congestive failure. Her period of observation in the hospital was only two days when she was taken home and died shortly thereafter. Post-mortem study was not obtainable.

*Toxicity.*—In the group of patients treated with prophylactic sulfadiazine we encountered no toxicity necessitating permanent cessation of treatment. One child complained of some dizziness and fatigue during the first weeks of taking the drug, but these symptoms subsided without withdrawal of sulfadiazine. In no case did blood counts show any total white cell count below 4,000 or polymorphonuclear cell count below 38 per cent. In a few instances, counts between 4,000 and 5,000 were found, and in other few instances, polymorphonuclear counts between 38 and 50 per cent. Where these occurred, blood counts were followed at frequent intervals, but all soon returned to normal range without stopping the drug. In only one child was the drug stopped for four days because of a low total white cell count (4,000), and then reinstituted without difficulty.

With the small daily dose of prophylactic sulfadiazine we did not encounter any renal complications. Rare red cells were seen in a few urine specimens and an occasional trace of albumin was reported, but it is significant that these findings were not persistent in any patient when another urine specimen was examined within a short period of time or on later examination.

#### DISCUSSION

In this group of inactive rheumatic subjects, results with sulfadiazine as a prophylactic agent against recurrences proved to be as satisfactory as those obtained from sulfanilamide. With closely matched groups, the incidence of a single recurrence in the treated group (1.2 per cent) in contrast to one probable and six definite recurrences in the control group (8.0 per cent) is significant. The relatively low rate of recurrence in the control group is of interest and may be partially explained as related to a rather low general incidence of rheumatic activity during the same time interval as observed both in the rest of the Bellevue Children's and Adolescent's Cardiac Clinics and on the wards of the Children's Medical Service.

Concerning administration of the drug, the use of less frequent doses once or twice a day with sulfadiazine as compared to twice or three times a day with sulfanilamide proved to be a distinct asset. Where daily medication must be taken regularly over a period of months and years, cooperation on the part of the patient is best when the number of daily doses is reduced to a minimum. Previously, sulfa-prophylaxis was discontinued during the summer and restarted in the fall.<sup>9</sup> In 1943, the continuous use of prophylaxis throughout the year was instituted, as we had observed a significant number of cases of active rheumatic fever, both initial and recurrent attacks, occurring during the sum-



mer months of several preceding years. This change also obviated the increased clinic and laboratory load necessary when reinstituting sulfa-prophylaxis in the fall.

Despite our good fortune in not encountering any serious toxic manifestations, it is to be emphasized that such should be watched for and that the total white cell and polymorphonuclear counts should be followed at least through the first two months of prophylactic therapy. Urine specimens should be examined for albumin and red cells at regular intervals throughout treatment.<sup>11</sup>

The possible danger of development and infection from sulfa-resistant strains of hemolytic streptococci was watched for following news of such developments in certain of the armed service camps. No such cases occurred during this study. It should be noted that this treated group is small and also that the individuals we dealt with lived in homes widely scattered throughout New York City. These two points are in important contrast to the tremendous numbers treated and the close, constant contact of camp conditions notable in the reports on development of sulfa-resistant strains following sulfadiazine prophylaxis in the armed forces.<sup>12, 13</sup>

#### SUMMARY

1. In fifty-one inactive rheumatic children and adolescents treated with prophylactic sulfadiazine for eighty-seven patient years, one recurrence of active rheumatic fever was observed. In an equal number of closely matched controls observed throughout the same time period, one probable and six definite recurrences of active rheumatic fever occurred.

2. No instances of sulfadiazine toxicity necessitating permanent discontinuance of treatment were encountered.

3. It would seem more protective to the patient and more convenient in a clinic group to maintain prophylaxis throughout the year.

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# THE CARDIOPATHY OF SICKLE CELL ANEMIA AND ITS DIFFERENTIATION FROM RHEUMATIC CARDITIS

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**I**N CLINICS such as our own where there is a considerable Negro population, the problem of differentiating between rheumatic heart disease and the cardiac manifestations of sickle cell anemia is often troublesome. Accurate distinction between the two diseases is important in deciding upon the proper management of the individual case.

The literature on heart disturbances in sickle cell anemia was reviewed in 1942 by Klinefelter,<sup>1</sup> who added twelve cases of his own. Klinefelter pointed out certain peculiarities of the disorder which serve to distinguish it not only from rheumatic carditis, but also from the changes found in other forms of anemia. Wintrobe,<sup>2</sup> on the other hand, feels that the changes are similar to, if not identical with, those found in other chronic anemias. In relation to diagnosis, perhaps the most important of Klinefelter's conclusions is that rheumatic fever and sickle cell anemia do not coincide in the same patient. While he apparently overlooked Walker and Murphy's report<sup>3</sup> in which both conditions were found at autopsy, proved exceptions to the rule appear to be exceedingly rare.

Nearly all reported cases of cardiopathy in sickle cell anemia have been in adults. In children, Hamman<sup>4</sup> reported a case in 1933, and King and Jane-way<sup>5</sup> another in 1937. The following case is reported because of the apparent infrequency of the disorder in children and because it illustrates the diagnostic difficulties.

## CASE REPORT

M. W., a 12-year-old Negro girl, was first seen at the Stanford Children's Clinic in 1944. Her presenting complaints began at the age of 9 years when she developed "aching joints all over the body." These were associated with a low-grade fever and extreme fatigue. She was taken to a hospital where the diagnosis of acute rheumatic fever with heart disease and sickle cell anemia was made, and bed rest ordered. Eight months later the joint pains and fever recurred and she was hospitalized again with the same diagnosis, spending the following two months in bed. From this time until shortly before we first saw her in 1944 she had had no symptoms other than being more easily fatigued than her siblings. Three weeks previously, she had complained of backache. At no time had she had swollen joints, jaundice, or abdominal distress. The family history revealed that three siblings aged 9, 13, and 19 years had died of "yellow jaundice." The mother did not have symptoms, although sickle cells were demonstrated in her blood. The patient was admitted to the Children's Ward of Stanford University Hospital on June 16, 1944.

Physical examination revealed a well-developed and nourished 12-year-old Negro girl in no acute distress. The skin showed no icterus. Examination of the head, including fundi, was entirely negative. There were large submandibular lymph nodes. The lungs were clear to percussion and auscultation. There was a prominent, diffuse pulsation seen in the fifth interspace one centimeter lateral to the midclavicular line. A systolic thrill was felt in this position. The heart sounds were clearly heard at the base with P<sub>2</sub> greater than A<sub>2</sub>. Only the first sound was well heard at the apex. A grade 4 systolic murmur was present over the entire pre-

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cordium with its maximum intensity over the lower part of the heart. No diastolic murmur nor third heart sound was found. The rest of the physical examination, including abdomen, back, and extremities was entirely negative.

Laboratory studies showed hemoglobin of 7.74 Gm. per cent, 2.32 million red cells with 7.5 per cent reticulocytes, and 14,900 white cells with normal distribution. Heavy sickling of the red cells was observed in the counting chamber. Erythrocyte sedimentation rate (Cutler) was 2 mm. per hour. Urine, blood Wassermann, stool, vaginal, and nasopharyngeal cultures were all negative. Venous pressure was 6 cm. of water; circulation time (decholin, arm-to-tongue), thirteen seconds. X-rays of the skeleton disclosed marked thickening of the cranial vault. The cardiac shadow was enlarged and "of mitral configuration with a markedly prominent left auricle which displaces the esophagus" (Fig. 1). The electrocardiogram revealed a P-R interval of 0.25 second and notched P waves in all leads. The RS-T segment was elevated in Leads II and III (Fig. 2). These findings have not changed in the many subsequent electrocardiograms. Stethograms taken June 13, 1944, showed a murmur occupying all of systole, and a less intense, early, diastolic murmur before and after a third heart sound (Fig. 3).

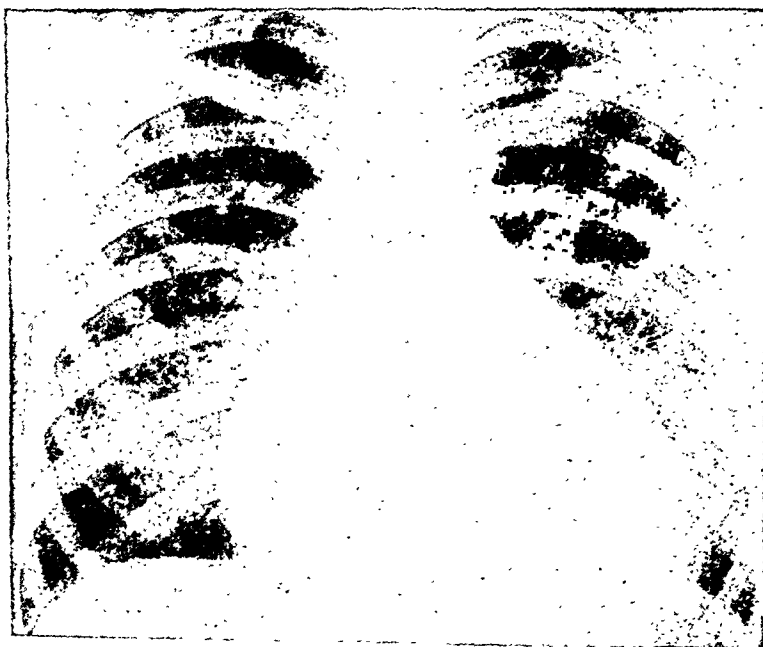
The patient was given several blood transfusions. While on the ward she had one sickle cell crisis, consisting of severe pain in the arms and back. This was relieved by morphine sulfate. She was dismissed on June 13, 1944, with a diagnosis of rheumatic heart disease and sickle cell anemia.

During the next nine months she was seen regularly in the Children's Clinic and was observed to be getting along fairly well on limited activity. There were brief episodes of backache, and toward the end of this period she was more easily fatigued. Her hemoglobin having fallen gradually from 11.4 Gm. per cent to 7.9 Gm. per cent, she was again admitted to the ward March 13, 1945, for transfusion. During this entry her antistreptolysin titer was found to be 100 units per cubic centimeter (normal) and her icterus index was 20 units. The sedimentation rate with low carbon dioxide tension was 21.5 mm. and with high carbon dioxide tension, 9 mm. per hour. The physical examination and other laboratory findings were similar to those of the previous entry. Because of the persistently low erythrocyte sedimentation rate and normal antistreptolysin titer, the diagnosis of rheumatic fever was questioned. It was felt that all the findings, including the prolonged P-R interval, were compatible with sickle cell heart. She was discharged March 23, 1945, with this diagnosis and it was decided that her activity at home needed only to be self-limited.

She has had four subsequent hospital entries for transfusions. It is of interest that she has had eleven of these, and the child herself would come voluntarily to the clinic requesting them. She told us that she developed loss of appetite, irritability, and extreme fatigue whenever her hemoglobin was low. In December of 1945, her heart was found to be 5 cm. wider by x-ray, and further enlargement was noted in the left auricle. The diastolic murmur previously demonstrated only by sound tracings had now become audible. Jaundice was first noticed by the patient in January, 1946. Her liver became palpable 3 fingerbreadths below the right costal margin in April of this year and subsequently could not be felt. Physical examination and stethograms repeated in June, 1946, showed, in addition to the early and middiastolic murmurs previously noted, a low-pitched presystolic murmur at the apex (Fig. 4).

#### DISCUSSION

The history in rheumatic infection and sickle cell anemia often displays similarities with respect to fatigability, failure to gain weight, dyspnea, pains in the extremities, and abdominal distress. The last of these may take the form of vague complaints with nausea and vomiting or may manifest itself by violent symptoms of pain, tenderness, and involuntary spasm.<sup>6</sup> We have seen instances of both diseases associated with the signs of peritonitis. Often a distinction can be drawn based on the location of pain in the extremities. Characteristically, it should be found in the joints in rheumatic fever and along the



A.



B.

FIG. 1.—A, Roentgenogram of the heart on Aug. 11, 1944, demonstrating diffuse enlargement. B, Roentgenogram of the heart in right anterior oblique view demonstrating backward displacement of the barium-filled esophagus by the left auricle.

course of the long bones in sickle cell anemia. It has been our observation that the children themselves usually refer their pain to *joints* so that we feel this is not often a helpful differential point. Conversely, many of our milder rheumatics complain of muscular pain. T. Duckett Jones<sup>7</sup> states that this is the rule in children. He feels that the typical migratory polyarthrititis with redness, heat, and swelling is encountered frequently in adults but infrequently in children. Of greater significance is the response of the pain to salicylates. Usually pain of sickle cell anemia requires more energetic sedation.

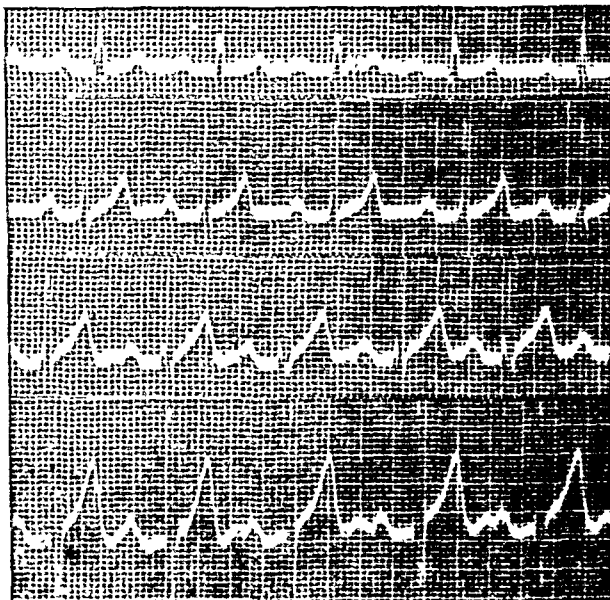


Fig. 2.—Electrocardiogram taken May 10, 1944. Note the P-R interval of 0.25 seconds, notched P waves, and elevation of R-ST segments in Leads II and III.

Careful evaluation of all the physical findings is of importance. Such features as jaundice, generalized lymphadenopathy, hepatomegaly, leg ulcers, and either a large spleen or a small, hard one are commonly found in sickle cell anemia and are not part of the syndrome seen in rheumatic fever. Conversely, developing heart disease associated with rheumatic nodules, erythema multiforme, or chorea, if present, make rheumatic fever more likely. The greatest confusion exists in respect to signs present in the heart. Both conditions may be associated with enlargement, tachycardia, third heart sounds, systolic and diastolic murmurs. Enlargement, although present in both instances, is attributable to different causes. In acute rheumatic carditis the myocardial damage produces dilatation leading to hypertrophy, or in rheumatic fever with mitral stenosis the abnormally produced pressure puts strain first on the left auricle and later on the right heart, causing enlargement of these parts. The best theory to explain the diffusely enlarged sickle cell heart appears to be that the long-standing anemia increases cardiac output and eventually such an overload leads to a dilatation and hypertrophy affecting all the chambers equally. On

auscultation the signs may be identical. Thus, in 1942, Klinefelter,<sup>1</sup> calling attention to the common practice of assuming that apical diastolic murmurs indicate mitral stenosis, analyzed eleven autopsies of patients, all of whom had sickle cell anemia and two in whom a secondary diagnosis of rheumatic fever was made. Actually, there were no examples of valvular scarring, although all the patients had had diastolic murmurs during life. He postulated a relative stenosis resulting from the failure of the mitral ring to expand along with the dilating myocardium. Earlier, Bland and associates,<sup>2</sup> in discussing the production of mitral murmurs in rheumatic fever, pointed out that even in this disease, presystolic murmurs may be heard in patients who prove at necropsy to have only

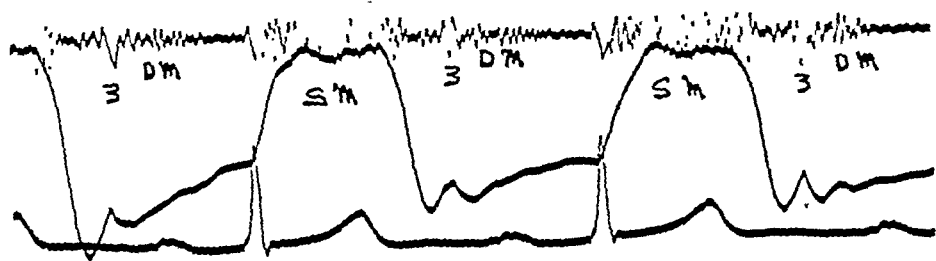


Fig. 3.—Stethogram at the apex on June 13, 1944, demonstrating a murmur which fills systole. An early diastolic murmur is shown both preceding and following a third heart sound.

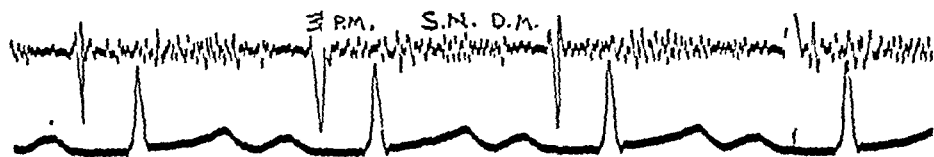


Fig. 4.—Stethogram repeated June 12, 1946, demonstrates the appearance of a presystolic murmur.

myocardial damage without valvular deformity. Care must be exercised, therefore, in making a diagnosis of mitral stenosis on the basis of a mitral diastolic murmur alone, since it may occur with either sickle cell or rheumatic heart disease and may not in either case represent a true valvular stenosis.

Laboratory studies are concerned primarily with demonstrating the presence of sicklemia. This can be accomplished without difficulty by merely observing the red cells in the counting chamber after shaking the pipette for ten minutes. If a patient has severe symptoms from his disease, it is usually not necessary to use special techniques to bring out the sickling nor make an exhaustive search for sickle cells. The procedure is done during a routine blood count and has proved to be a practical aid. Leucocytosis, another finding common to both diseases, may be misleading. Perhaps because we see milder rheumatics in California, leucocytosis has actually been present with greater regularity in our sickle cell anemias. Reticulocytosis is expected with the latter conditions. The sedimentation rate is of interest because an increased rate is usually considered to be the most constant of all laboratory tests for active rheumatic fever. If intravenous blood is drawn in the routine manner and the

sedimentation tube is filled without delay, thus not allowing much oxygenation, the sedimentation rate will be greatly decreased in the presence of sickle cell anemia. This point was well demonstrated in 1944 by Winsor and Burch,<sup>9</sup> who showed that the blood in sickle cell anemia could be made to settle more rapidly after saturation with oxygen and to slow down markedly with carbon dioxide. The sedimentation rate is not so altered in patients with other diseases. This may be a useful short cut in diagnosis if a patient suspected of having rheumatic fever has an erythrocyte sedimentation rate of only 1 to 3 mm. per hour. The notable exception to this rule occurs during acute cardiac decompensation, which in itself lowers the sedimentation rate as the result of hemoconcentration.

Electrocardiographic findings show similarities in respect to increased P-R interval, but this is more frequent and perhaps more marked in sickle cell anemia. Roentgenograms are helpful in demonstrating the bone changes in sickle cell anemia as well as the size and configuration of the heart. As mentioned above, a diffusely enlarged cardiac silhouette is the rule with sickle cell hearts. Perhaps the best differential criterion is the mere presence of sickle cell anemia, which creates a presumption that the cardiac disorder is not rheumatic.

#### CONCLUSION

A case of sickle cell cardiopathy in a 12-year-old Negro girl is reported. The differentiation of this condition from rheumatic carditis depends on the failure of pain in the extremities to respond to salicylates, the finding of jaundice, lymphadenopathy, or an abnormal spleen, the demonstration of anemia, reticulocytosis and sickling of the red cells, a slow erythrocyte sedimentation rate, diffuse cardiac enlargement, a greatly prolonged P-R interval, and the characteristic bone changes associated with sickle cell anemia.

Rheumatic carditis appears to be extremely rare in patients with sickle cell anemia.

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# FACTORS IN THE ETIOLOGY OF CONGENITAL HEART ANOMALIES

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**A**MONG the theories concerning the causation of congenital anomalies of the heart, the most widely accepted is that in the great majority of cases the proximate cause is arrest or imperfect development of the heart in early intra-uterine life. The question of the primary cause remains unanswered. Possible causes are environmental factors that affect the growing embryo after fertilization has taken place, and intrinsic or inherited factors from either parent, due to defective germ plasm prior to fertilization. These factors will be separately discussed in the light of data obtained from the cases seen in the Infants' and Children's Hospitals of Boston.

## ENVIRONMENTAL FACTORS

Disturbance of development occurring between the fifth and eighth weeks of intrauterine life, the period when the most rapid growth of the cardiac septa and the most complex rotation of the cardiac chambers take place, is the chief cause of the great majority of cardiac anomalies.<sup>1</sup> Maternal disease at this stage of pregnancy may be expected to play a major role in inducing such faulty development. In 1941, Gregg<sup>2</sup> published the first report of congenital anomalies in infants born of mothers who had contracted rubella in the early weeks of pregnancy. Since that time, several reports have appeared implicating one of the virus diseases in the first trimester of pregnancy. The literature on this subject has been reviewed and summarized by Albaugh<sup>3</sup> and Conte and his co-workers.<sup>4</sup> Certain questions, however, remain to be answered satisfactorily.

The first of these questions is as to the frequency with which maternal virus infections in early pregnancy are followed by offspring with congenital anomalies. Fox and Borton<sup>5</sup> have recently reported their observations with rubella complicating early pregnancy, showing that a considerable proportion of offspring escaped congenital anomaly. Nevertheless, we feel that, pending extensive observations to the contrary, it must still be considered that in the case of rubella, at least, infection in the early weeks of pregnancy carries a high likelihood of congenital anomaly as a sequel. Meanwhile, regarding virus and other exanthematous infections besides rubella, we have investigated the records of all women admitted to the South Department, or the contagious unit,‡ of the Boston City Hospital from 1936 through 1945, in an effort to determine the frequency with which these other conditions have been followed by anomalous offspring. All patients with virus and other exanthematous

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‡Access to these records was offered through the courtesy of Dr. Edwin H. Place.



diseases were studied. Out of 1,387 women admitted with various virus and other exanthematous diseases, seventeen were pregnant, and of these only six were in the first four and one-half months of pregnancy. Our field of investigation has thus been so narrowed that we find it necessary to apologize for the brevity of this series of cases. The offspring of these six patients were followed. One mother had mumps in the second month of gestation, another had measles in the third month, and the other four had scarlet fever at one and one-half, two, two, and four and one-half months, respectively. Three of the mothers with scarlet fever had received sulfadiazine, in each case for five days, the dosage being 4 Gm. initially by mouth followed by 1 Gm. doses every four hours. In two of these cases the drug was withdrawn on the fifth day because of intolerance to it. The mother who had scarlet fever at four and one-half months gestation was exposed to measles and received gamma globulin because she was susceptible to the disease. Clinically, measles did not appear. In these six verified cases of maternal infection in early pregnancy, it is notable that none of the offspring developed a congenital anomaly except for a possible minor congenital obstruction of the lacrimal duct in the child of the mother who had measles in the third month. These findings are listed in Table I.

TABLE I. OFFSPRING OF MOTHERS WITH VIRUS AND OTHER EXANTHEMATOUS DISEASES IN EARLY PREGNANCY

CASE NAME	DISEASE OF MOTHER	REMARKS	MONTHS PREG-NANT AT TIME OF DISEASE	BIRTH AT TERM (T) OR PREMA-TURE (P)	SEX RACE	BIRTH WEIGHT (LB.)	ABNORMAL-ITIES IN OFFSPRING
1 L. A.	Mumps	Bilateral; submaxillary and left parotid glands	2	T	M Negro	7½	None
2 C. M.	Rubeola	Mild	3	T	F White	8	Obstruction of right lacrimal duct
3 H. W.	Scarlatina	Treated with sulfadiazine for 5 days	1½	T	F White	6½	None
4 W. M.	Scarlatina	Also had bronchial asthma	2	T	F White	6½	None
5 J. M.	Scarlatina	Treated with sulfadiazine for 5 days	2	P (?)	M White	9	None
6 M. H.	Scarlatina; exposure to rubeola	Gamma globulin; sulfadiazine for 5 days	4½	T	F White	7½	None

Another question is as to the frequency with which mothers of children with congenital heart anomaly give a history of infection or exposure to noxious agents in the course of pregnancy. In an attempt to answer this question, the records of all patients with congenital heart disease seen in the Infants' and Children's Hospitals during the decade from 1936 through 1945 were reviewed. The records of 434 patients were sufficiently detailed in this regard to allow reliable conclusions to be drawn. In nine of these cases, maternal virus infection was discovered, all in the first trimester of pregnancy (Table II). Moreover, all of these patients were observed during the last four

TABLE II. PATIENTS WITH CONGENITAL HEART ANOMALIES WITH HISTORY OF MATERNAL VIRUS DISEASES

NAME	DISEASE IN MOTHER	MONTHS PREGNANT AT TIME OF DISEASE	BIRTH AT TERM (T) OR PREMATURE (P)	SEX	ANOMALIES AND CRITERIA FOR DIAGNOSIS		CYANOSIS	OTHER CONGENITAL ANOMALIES	
								Present	None
1 G. B.	Anterior polio-myelitis	2	T	M White	Heart enlarged; soft systolic murmur along left sternal line; x-ray showed large, rounded heart		Present	None	
2 C. P.	Rubella	1	T (?)	F White	Tetralogy of Fallot (operation by Dr. Blalock)		Present	Bilateral cataract	
3 E. K.*	Rubella	3	T	F White	Rough systolic murmur, maximum over precordium, best heard some distance away from heart; x-ray showed globular heart		Absent	Bilateral cataract	
4 P. S.	Rubella	2½	T	M White	Harsh to-and-fro murmur in pulmonary area, with grade II murmur over apex, x-ray showed globular heart with broad base; interventricular septal defect		Absent	Congenital cataract of left eye; complete cleft of palate; malformation of right fourth rib; father had complete harelip and cleft palate	
5 L. R.*	Rubella	1	T	F White	Typical patent ductus arteriosus (divided later by Dr. Gross); x-ray showed typical signs, & interventricular septal defect		Absent	None	
6 W. M.	Exposure to rubella (susceptible)	2	T	M White	Pulmonary stenosis; interventricular septal defect		Present	None	
7 A. H.	Virus grippo	3	P	M White	Interventricular septal defect; x-ray showed enlarged heart; E.K.G. showed right axis deviation		Absent	None	
8 L. C.	Virus grippo	2	T	F White	Large interventricular septal defect; x-ray showed enlarged heart		Present	Tracheoesophageal fistula	
9 V. B.	Rubella	3	P	M White	E.K.G. showed right axis deviation; patent ductus arteriosus		Present	Bilateral cataract	

\*These were Dr. John Davies' private patients, treated in the Children's Hospital. Dr. Davies has observed three other such instances of congenital anomalies following pregnancy complicated with rubella. We are grateful for his permission to refer to these cases in this report.

years, possibly because in this period closer search has been made for any history of such infections.

The occurrence of anterior poliomyelitis in the second month of pregnancy followed by congenital anomaly in the offspring is, we believe, the first of its kind to be reported. A summary of this case follows:

G. B., a white, male infant, was the only child of a 19-year-old mother. A diagnosis of anterior poliomyelitis was made during the second month of pregnancy, and the mother was treated in an outside hospital. No residual paralysis remained. There was no other family history of congenital anomaly. The infant was born at full term with a normal delivery. The birth weight was 6 pounds 6 ounces (2.9 kg.). The patient was admitted at 9 days of age because of cyanotic spells since birth.

Physical examination showed a cyanotic, slightly jaundiced baby with moderate dyspnea. The conjunctival vessels were extremely prominent and engorged. The chest was asymmetrical, with prominence of the right side, where the breath sounds were louder than on the left. The heart was greatly enlarged on percussion, mostly to the left. A soft, systolic murmur could be heard irregularly along the left sternal border. The liver was palpable one fingerbreadth below the right costal margin, and the spleen could not be felt. The laboratory findings were within normal limits. Roentgenograms of the chest showed that the heart was greatly enlarged, full, and rounded in appearance, suggesting a severe type of congenital malformation, probably with a large interauricular septal defect. The electrocardiogram showed left axis deviation, -50 degrees, R<sub>1</sub> greater than R<sub>2</sub>, and T<sub>1</sub> flat or depressed.

Review of the literature indicates that anterior poliomyelitis is by no means a rare complication of pregnancy,<sup>6-8</sup> yet since there have been no previous reports of congenital anomaly in the offspring of such pregnancies, in spite of widespread current interest in the subject, we feel that pending further evidence, the case just cited must be evaluated with caution.

In eight other cases the mother had a nonexanthematous bacterial infection during pregnancy. These cases are listed in Table III. The significance of such infection is uncertain. In addition to the mothers listed in the table, two had suffered from acute rheumatic fever and one from chorea during the first trimester, and their children were born with heart disease. In two cases of

TABLE III. PATIENTS WITH CONGENITAL HEART ANOMALIES WITH HISTORY OF MATERNAL BACTERIAL INFECTION

CASE SEX	DISEASE IN MOTHER	MONTHS PREGNANT AT TIME OF DISEASE	ANOMALY
1 F	Pneumonia	? early months	Congenital heart disease (no cyanosis)
2 F	Pyelitis	Early months	Dextrocardia (cyanotic)
3 F	Pyelitis	Early months	Congenital heart disease (no cyanosis)
4 F	Mild pyelitis	?	Congenital heart disease (no cyanosis)
5 F	Pyelitis	Early months	Congenital heart disease (cyanotic)
6 M	Strep. throat	First month	Congenital heart disease
7 M	Infected teeth	?	Cyanotic; great vessels transposed
8 M	Cystitis	Two months	Congenital heart disease; cyanotic and mentally retarded

congenital heart disease, the mother was found to be syphilitic. In one case the mother had had a severe ptomaine poisoning during the first month of pregnancy and was seriously ill for at least a week; her child was born with a probable Eisenmenger complex. Four mothers of children with congenital heart disease gave a history of allergic manifestations during the early part of pregnancy. One, an army nurse, had an appreciable degree of dermatitis on the hands during the first three months of pregnancy, probably an allergic manifestation due to the handling of emetine. Another suffered three attacks of hives during pregnancy, being allergic to lobster, pork, and cucumbers. Two other mothers had continuously suffered from attacks of asthma during pregnancy. The cause of allergy was not determined. In five patients severe trauma was present in the first trimester of pregnancy. In one case the mother developed thyrotoxicosis two months prior to conception, and during the second month of pregnancy a subtotal thyroidectomy was performed. The baby had a probable Lutembacher syndrome (interauricular septal defect with mitral stenosis). In still another case the mother was receiving thyroid extract for a low metabolic rate throughout pregnancy. In three cases the mother had been exposed to lead (while painting) during the early part of pregnancy.

#### INHERITED OR INTRINSIC FACTORS

The importance of heredity as a factor in congenital anomalies is undoubtedly great, but this is obscured by the propensity of such defects to cause early fetal death and resultant abortion. However, the frequency of other associated anomalies in other members of the family is indicative of the importance of heredity in congenital cardiac diseases. Among 720 patients with definite congenital cardiac anomalies, the records of 680 contained adequately detailed family histories. Of these 680 patients, sixty-seven (10 per cent) showed congenital heart defects or other anomalies in other members of the family. In twenty-seven patients (4 per cent) other siblings were involved, and in one, both identical twins had apparently similar cardiac anomalies. Various studies,<sup>9, 10</sup> although the statistics are not rigidly comparable, indicate that the incidence of congenital malformations in the general population is from less than 1 per cent to slightly more than 2 per cent. Among anomalies elsewhere in the body were the following: harelip and cleft palate, cerebral deficiency, imperforate anus, rectovaginal, rectoperineal, and tracheo-esophageal fistulas, malformation of digits, hydrocele, cataract, microphthalmia, micrognathia, microglossia, dwarfism, nephromegaly, Meckel's diverticulum, pyloric stenosis, accessory spleen, bilobed spleen, deformity of spine, ribs, and sternum, meningocele, congenital atresia of the bile ducts, accessory ear tabs, torticollis, and the Klippel-Feil syndrome. In forty-two patients with congenital cardiac defects (5.8 per cent), Mongolian idiocy was found to be an associated finding.

In considering other types of inherited abnormalities, the possibility of paternal exposure to industrial poisons must be included. Most of our information concerning the damage to the next generation that is caused by in-

dustrial poisoning has been drawn from the lead trades.<sup>11</sup> Statistics gathered by Hamilton<sup>11, 12</sup> show that an unusually large proportion of children of fathers exposed to lead are stillborn, but the evidence is not conclusive. Data in the European literature indicate that the incidence of miscarriages and stillbirths is excessively high in the wives of men working in lead industries.<sup>11</sup> Weller<sup>13</sup> has shown that male guinea pigs exposed to lead were not sterile but the young fathered by them were weak and underdeveloped. Their subsequent development was slow, and the number of deaths during the first week of life was high. We have made a practice of inquiring into the possibility of paternal lead exposure in all congenital cardiac cases in which information was obtainable.\* In 645 of the present series of 720 cases the occupation of the father was mentioned, and, interestingly enough, in 61 cases (9.5 per cent) the occupation involved one of the hazardous lead trades, such as painting or working in battery plants. Trades only occasionally permitting the handling of lead in nondangerous physical forms are excluded.

With the help of the Massachusetts Department of Labor and Industries and the kindness of Dr. Harriet L. Hardy, a survey of the incidence of congenital anomalies in children of workers exposed to lead hazard will be carried out by one of the authors (H. G.).

#### SUMMARY AND CONCLUSIONS

The possible factors in the causation of the congenital anomalies of the heart are discussed.

It is shown that mumps, rubeola, and scarlet fever during early pregnancy do not constantly produce offspring with anomalies.

Of 434 patients with congenital heart disease, with detailed histories concerning the course of pregnancy, one gave a history of anterior poliomyelitis, five of rubella, one of exposure to rubella, two of grippe, two of rheumatic fever, one of chorea, two of syphilis, and eight of bacterial infection during the early months of pregnancy. In four patients there had been allergic manifestations, in one, severe ptomaine poisoning, in two, disturbances of thyroid gland, in three, exposure to lead, and in five, trauma. The vast majority of mothers had had an uneventful pregnancy. It thus appears that disease and the presence of noxious agents during pregnancy could possibly account for only a small proportion of cases with anomalies, and further investigation, to which it is hoped the present report may make a small contribution, is necessary to explain the etiology of these conditions.

The importance of heredity in the etiology of congenital cardiac diseases is considered and the family histories of 680 cases are summarized with reference to the occurrence of anomalies in other members of the family.

The high incidence of paternal lead exposure was considered impressive and will be the subject of further investigation.

\*The original suggestion for this inquiry had come from Dr. Paul W. Emerson.

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## DACRYOSTENOSIS

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**M**OST pediatricians have been called upon, at one time or another, to prescribe for the baby whose tears overflow the conjunctival sac. There is a school of ophthalmology which claims that these patients should be treated by operation. We have observed a series of about 200 infants in which the natural history of the condition would indicate that such radical measures are rarely necessary.

This condition is called epiphora, an overloading of the conjunctival sac with tears. The term dacryostenosis is coming into more common usage because of the usual embryologic explanation.

The first appearance of the anlage of the nasolacrimal duct is in the 12 mm. embryo. There is a ridgelike thickening of the epithelial lining of the nasolacrimal groove which extends from the inner angle of the orbital fossa to the primitive olfactory fossa. The ridge becomes cut off from the surrounding epithelium, and sinks as a cord into the underlying mesoderm. Subsequently, due to differences in growth, this cord may be separated from the ectoderm of the nasal cavity and later join up again. As the eyelids form, the cord is found passing medially from the inner canthus, then down to the nasal fossa. It may have gaps in it. Canalization begins at about the 50 mm. stage and normally is completed before birth. One of the last changes in the fetus before birth is the final degeneration of the center of this cord where it opens into the nostril below the lower turbinate under a fold of mucous membrane known as the valve of Hasner. For this reason, delay in opening is one of the common anomalies seen after birth.

During the first few weeks of life there is little secretion of tears. When they do appear, they do not drain away as rapidly in dacryostenosis as in the normal condition. The mother complains that one or both of the baby's eyes tends to water. She is more likely to complain if the condition is unilateral, because then she has a means of comparison.

If the lacrimal sac is irrigated at this stage with a Ewing syringe, considerable epithelial debris and/or a mucous plug may be dislodged. This has led observers to believe that many cases of obstruction are due to accumulation of the products of degeneration. A further corroboration is the fact that many of these cases clear up spontaneously with no treatment whatsoever. This usually occurs during a good cry, when there is a copious supply of tears and much blinking, with compression of the lacrimal sac by the forceful closure of the eyelids, such as during attempted examination of the eyes of the small baby in the doctor's office.

To what extent 2 per cent silver nitrate instilled into the eyes of the newborn is a factor in this condition is an open question. There is no doubt as to its

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efficacy in reducing ophthalmia neonatorum, which is still the greatest cause of blindness. For this reason its use must not be challenged until something better is proved. Anyone who has had it instilled in an eye in later life knows how much it stings. Those who work in maternity ward nurseries are familiar with the chemical conjunctivitis which it causes. The law in Alberta permits the use of fresh, 40 per cent Argyrol instead, but it is not nearly so efficacious and is largely being discarded. Last spring the pediatricians in Toronto persuaded the Ontario government to permit the use of penicillin. Dr. E. A. Morgan tells me that not only has the chemical conjunctivitis disappeared, but that it is his impression that there is a great reduction in the number of cases of epiphora seen.

Some writers have stressed the importance of stenosis along the course of the canal, presumably at the sites where the continuity was broken during fetal life, as at the nasal end and at the entrance and exit of the lacrimal sac. Stenosis facilitates the accumulation of debris. Frequently, in irrigation, the continuity is established at the first attempt and the epiphora disappears.

But not all cases clear up so easily. The condition may persist for many months as if the process of canalization were delayed, in which case the infant may continue to have a membrane over the lower end of the canal. This prevents proper drainage and causes further accumulation of debris, and secondary infection with organisms of low virulence or invasion with leucocytes may result. Such infants are brought to the office with the complaint that the eyes are sticky, especially on awakening in the morning. In these cases the purulent material has formed in sufficient quantities to back up into the conjunctival sac during sleep and evaporate on the lid margins. It may be necessary to bathe the eye before the baby can open it. There is little or no redness or swelling, because the walls of the canal have not been invaded by an inflammatory process. After the eye is bathed, a small drop of pus can sometimes be expressed by pressure on the lacrimal sac.

It is concerning this group of cases that there has been a divergence of opinion as to the correct procedure. The ophthalmic surgeons have insisted, with good argument, that probing, and hence breaking through a persistent membrane or dilating a stenosis, is the method of choice. Others have maintained that more conservative methods of treatment give satisfactory results in the vast majority of cases. Since this difference of opinion was first drawn to my attention I have been interested in following the results of conservative treatment. Certainly the number of cases referred for probing has been greatly reduced. Because most of the literature on the subject is written by ophthalmologists whose patients undoubtedly require operative interference, we have kept under observation a series of pediatric patients with this complaint, to determine the natural history of the condition.

The conservative treatment consists of keeping the eye clean with boracic solution (in some cases using an antiseptic in the conjunctival sac) and pressure over the lacrimal sac. Irrigating the conjunctival sac of the small baby cannot be done efficiently by the mother, and about all that it accomplishes is cleanliness of the eyelids and an improved appearance.



Silver solutions are contraindicated because of the danger of argyria. Parents should be warned against using such preparations as argyrol, because they are tempted to continue the treatment indefinitely in a condition which may be chronic. They get a false sense of security with antiseptic eye drops because when they are discontinued, the formation of pus seems to recur, probably due to an increase in growth of the organisms that invade the stagnant fluid.

The crux of the conservative treatment lies in the pressure over the lacrimal sac. This is applied firmly with the washed fingertip, with a rocking motion from above downward at the inner canthus in an attempt to expel the contents of the sac down the nasolacrimal duct into the nose. Since the baby usually expresses objection to such close proximity to his eyes by crying, there is a copious supply of tears. The process is repeated by the mother for about a minute two or three times a day. It is the same principle as the rubber bulb pump. The theory is that this measure stimulates the flow down the nasolacrimal duct in a forceful manner, keeping it clear of debris, and stimulates its development as a drainage tract. Ophthalmologists have assured me that it is quite possible with one forceful expulsion to rupture a persistent membrane at the valve of Hasner. Some writers urge repeated office irrigation of the duct with normal saline, but in a busy pediatric practice this has not been feasible, and it has been my observation that ophthalmologists to whom these cases have been referred have preferred to probe and dilate the duct rather than to drag out the treatment in such a time-consuming manner.

When a true dacryocystitis develops, it is a case for the ophthalmologist. I have only one such case on record. It is my impression that I have seen several others that were not under treatment by our department. They were forwarded at once to the ophthalmologist without starting a record. The treatment is adequate drainage by probing or by incision and drainage of the lacrimal sac. The drain in such an incision must not be left in too long a time as it predisposes to a lacrimal fistula. This is an argument for drainage by probing. Heat is applied as warm compresses. Recently, chemotherapy has taken an important place in the treatment of this condition. There is growing a school of thought which claims that the infection should be overcome by chemotherapy before dilatation by probing is undertaken.

Eliminating the one case of dacryocystitis, we have followed up 203 patients with dacryostenosis. Eleven of these (5.4 per cent) have been treated by probing. In comparing this with Hardesty's series of sixty patients in which 66 per cent required probing, we must bear in mind the difference between a pediatric practice in which the mother brings every little complaint to the doctor and an ophthalmic practice with many referred cases.

Of the total 203 patients with dacryostenosis, thirty-four were seen before conservative treatment became routine in our pediatric department, and 169 were seen since. Of the eleven patients treated by probing, six (17.6 per cent of the thirty-four) occurred in the former series, and five (2.9 per cent of 169) occurred in the latter.

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In the series of thirty-four patients in the first period, seven were referred to an ophthalmologist. As stated above, six had the ducts dilated by probing under anesthesia. The seventh recovered while the family was considering the ophthalmologist's advice to operate. This patient and two others recovered while receiving only mild antiseptics in the eyes. Four recovered without any treatment and four recovered while receiving local antiseptics and massage. The remaining seventeen recovered with only massage of the inner canthus.

Of the six patients treated by probing in the first series, three might easily have responded to conservative treatment if it had been tried. They were 4, 7, and 10 months of age. The fourth was a 10-year-old boy. The fifth patient required probing twice. The sixth was an 8-month-old baby whose parents insisted on something definite being done at once.

Of the five treated by probing in the second series of 169, one patient required dilatation twice. Two were referred to an ophthalmologist when first seen by a new associate who was unfamiliar with the routine, and promptly received dilatation. One patient was referred and probed one month after being placed on conservative treatment at 4 months of age by the same associate, but I am unable to determine how conscientiously the treatment was carried out. The fifth case was a boy of 8 months who was not placed on conservative treatment but who required a circumcision. Advantage was taken of the anesthetic to dilate his duct.

Thus, in the whole series of 203 patients there were only three with positive indications for operative interference.

Of the 192 patients whose conditions cleared up without operative interference 149 (77.6 per cent) had recovered by three months of age, twenty-six (13.5 per cent) recovered by 6 months of age, twelve more cases (6.3 per cent) recovered by one year and the remaining five (2.6 per cent) cleared up during the second year. From this it would appear that nature takes care of most of these cases of delayed development.

#### CONCLUSION

Cases of simple dacryostenosis can be treated conservatively with success by the pediatrician until well after the first year. Cases of dacryocystitis should be referred at once to the ophthalmologist for treatment.

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## INTESTINAL OBSTRUCTION OF THE NEWBORN

A REPORT OF FIVE PATIENTS SUCCESSFULLY RELIEVED BY SURGERY

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**I**NTESTINAL obstruction of the newborn may be caused by atresia of the bowel, which signifies complete obliteration of the lumen, or stenosis, which signifies incomplete obliteration of the lumen. The bowel may also be compressed from without. This is extrinsic obstruction. Our patients are three with atresia and two with extrinsic obstruction.

A few brief sentences will adequately describe the symptoms and signs observed in these five newborn infants with intestinal obstruction. The generalizations deduced from them are greatly strengthened by the fact that these observations largely coincide with those made by Ladd<sup>1</sup> on a much larger series.

The diagnosis rests largely on two important symptoms. The first is vomiting, which is unlike ordinary vomiting of the newborn. It begins early, usually the first day of life. It is frequent, copious, persistent, bile stained, and usually nonprojectile.

The pediatrician is likely to see the bile-stained vomitus in the basinet. The vomitus is more likely to roll out than to shoot out. One is at once struck with the fact that this is no ordinary vomiting of the newborn. The nurse offers the information that the baby began to vomit soon after birth. The bile in the vomitus attracts attention. The obstruction is seldom proximal to the ampulla of Vater. This occurred only once in Ladd's entire series of fifty-two patients with congenital atresia of the bowel.

The second cardinal symptom is distention of the abdomen. It may be distended at birth, but usually is not until after birth, and distention may be so slight that it scarcely attracts attention, or it may be enormous. The amount of the distention depends, at least in part, on the location of the lesion; the lower the lesion the greater the distention. Visible, deep, peristaltic waves, when present, are pathognomonic of obstruction. They were a prominent feature in our patients with atresia except the one with perforation. They were lacking or inconspicuous in the two patients with extrinsic obstruction. In depth, these waves resemble those of pyloric stenosis. They may be in any portion of the abdomen. Hypertrophy and distention above the point of atresia are so great that the location of the distended loops is not a reliable guide to the anatomic site of the obstruction.

Roentgenograms are helpful, but the barium sulfate meal is usually not necessary to establish diagnosis. It is dangerous and causes considerable delay when time is very valuable. It is an added insult to a gastrointestinal tract which is already badly out of adjustment. Moreover, the flat film usu-

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ally yields the desired information. If the lesion is atresia and is high in the gastrointestinal tract, both the stomach and upper bowel may appear as huge gas bubbles, as in Case 3. If atresia is lower in the bowel, numerous gas distended loops are likely to cover the film, as in Case 2. If the obstruction is not complete, gas will be distributed throughout the tract, as in Cases 1 and 5.

The time element is of paramount importance. The consultant seldom sees these babies before the third day, while ordinarily they must be operated on by the fourth day if the issue is to be successful. Diagnosis must be made promptly. The pediatrician should secure the services of a surgeon who is skilled in infant surgery.



Fig. 1.—Case 1. Photograph of 5 cm. enteric cyst with resected portion of the jejunum laid open. Note that it is closely bound to the cyst.

#### CASE REPORTS

**CASE 1.**—Baby P. was a full-term male infant born in the Ingalls Memorial Hospital, Harvey, Ill. on Nov. 14, 1943. Consultation was requested on the third day of life, when he appeared normal except for dehydration from almost continuous vomiting of a thin, light green fluid. Vomiting was not projectile. He lost one pound, one ounce in the first three days of life. On the fourth day he was transferred to St. Luke's Hospital, Chicago, and improved with supporting measures. Besides meconium he passed a little bile-stained mucus. This led to a diagnosis of *stenosis* rather than *atresia*. We temporized, hoping for improvement. Delay was a serious error. Peristalsis became prominent, the abdomen distended, and the baby's condition grew worse. A barium sulfate meal was given on the seventh day with inconclusive results, and repeated on the eighth day. Obstruction was reported and operation was performed on that day.

A firm, globular, enteric cyst, 5 cm. in diameter, lay in the left upper quadrant (Fig. 1). The cyst wall contained all layers of the small bowel but it did not communicate with the lumen of the bowel. The proximal jejunum, before rising over this cyst, was folded on itself beneath it. This almost completely obliterated the lumen. Apparently, nothing had passed this point except the bile-stained mucus. Struggling against this obstruction, the jejunum had completely severed itself into two portions. The barium must have added materially to the shearing action of peristalsis in severing the bowel. The distal, severed end of the jejunum was closely bound to the cyst; the proximal end lay loose in the abdomen, which was filled with bowel content and barium sulfate. A side-to-side anastomosis was made and the abdomen closed.



Fig. 2.—Case 2. Roentgen-ray film of the abdomen soon after birth, showing marked distention. The gas-distended loops which largely fill the entire abdomen were of the upper gastrointestinal tract.

The postoperative condition was very poor and grew even worse. We ordered 2½ grains of sulfadiazine to be given subcutaneously. By error, 2.5 Gm. or 37 grains were injected. Severe nephritis followed, characterized by generalized edema with a large number of red cells and casts in the urine. In addition to this catastrophe the wound suppurated and opened widely. The baby almost eviscerated. After the baby's survival of these events, matters gradually improved. The edema disappeared two weeks after the onset of nephritis and the urine returned to normal after an additional two weeks. The baby left the hospital six weeks after operation, weighing 3 ounces less than at birth.

At the age of one year he returned to the hospital for observation. A complete x-ray study of the gastrointestinal tract with barium sulfate revealed no abnormality. He was normal except for some deformity of his belly wall.

CASE 2.—Baby S. was a full-term male infant born at St. Francis Hospital, Blue Island, Ill. at 4:30 P.M., July 13, 1944, and was first seen by us sixty-eight hours after birth. Three hours after birth he began vomiting a copious amount of bile-stained fluid. The abdomen was greatly distended at birth (Fig. 2). This was noticed in the delivery room. Four large loops of bowel were observed in vigorous peristalsis. The diagnosis was obstruction of the bowel, probably atresia. We advised against giving barium sulfate. The baby was operated upon three hours later or seventy-one hours after birth.



Fig. 3.—Case 2. Note also smaller distal defect of ileum. Note rounded end (a) without an attached mesentery of the proximal defect (b) and the herniation occurred.

At a point about 30 cm. below the ligament of Treitz the ileum ended in a blind, rounded end. Above this point, the bowel was enormously dilated and markedly hypertrophied to 35 or 40 mm. in diameter. The distended gut largely filled the abdomen. Distally, the ileum and colon were collapsed. They contained a light green, inspissated meconium which did not pass until after operation. The ileum here measured 7 to 9 mm. in diameter and began with a rounded end. There was no connection between the two portions, not even a chord. In addition to this deformity there were two large defects in the mesentery (Fig. 3). A narrow, fibrous band representing mesentery lay between the two defects, and another narrow, fibrous band connected the proximal tip of the distal portion of ileum to the root of the mesentery, thus representing another segment of mesentery. Neither of these mesenteric rudiments contained pulsating vessels. Through the distal and smaller mesenteric defect the terminal ileum, cecum, and ascending colon had herniated from anterior to posterior. There was impending perforation in the portion of the ileum corresponding to the middle of the lower mesenteric defect. This was probably due to the tension of the herniation.

The hernia was reduced, and the bowel divided at the site of the impending perforation. The segment of bowel between this point and the point of atresia was resected by simple ligation of the two bands of rudimentary mesentery and a side-to-side anastomosis

was accomplished. A catheter was placed in the bowel by the Witzel method above the anastomosis and brought out of the upper angle of the wound, which was closed in layers. The resected bowel measured 118 cm. (Fig. 3). This was estimated to be about one-half of the small bowel present.



Fig. 4.—Case 2. Photograph of autopsy specimen showing ostomy between the upper and lower portions of the ileum. Note marked contrast in size even after some equalization.

*Postoperative Course.*—Meconium passed per ano on the fourth day. The catheter was removed on the sixth day. The fistula closed spontaneously on the fourteenth day. The baby developed a celiac-like syndrome, taking an unusually large amount of food and discharging frequent thin, foul smelling stools containing fat. For a time the baby gained slowly, attaining a maximum weight of 6 oz. above birth weight. Lung infections were frequent, suggesting pancreatic disease. On the eighty-third day of life the baby was transferred to St. Luke's Hospital, Chicago. A barium sulfate meal showed a lagging at the site of anastomosis. The baby had adequate stools, however, as indicated by the fact that the abdomen from this time on diminished in size adjusting toward the normal proportions. Fat disappeared from the stools and abdominal distention became less. Nevertheless, the baby continued to lose weight and died on the one hundred twelfth day of life with signs of terminal lung infection, weighing 6 oz. less than at birth.

*Autopsy.*—Death was due to inanition and terminal bronchopneumonia. The diameter of the bowel below the ostomy had doubled, measuring 15 mm.; that above had decreased about one third, measuring 30 mm. except for a pouch just proximal to the ostomy. Thus the two diameters seemed to be equalizing themselves (Fig. 4). The entire remaining small bowel measured 210 cm. This is much greater than the estimated length at the time of operation. The pancreas was essentially normal.



Fig. 5.—Case 3. Roentgen-ray film of abdomen before operation. Note two large gas bubbles largely filling the abdomen. One represents the stomach; the other, the duodenum.

**CASE 3.**—Baby B. was a full-term male infant born at the Roseland Community Hospital, Chicago, July 4, 1944. He was seen in consultation thirty-four hours later. The presenting symptom was vomiting. It was frequent and persistent, occurring every few minutes, and began a few hours after birth. The vomitus was bile stained. The baby was dehydrated, and in three days lost 1 lb., 6 oz. He passed large amounts of meconium. For this reason the attending physician was reluctant to accept the consultant's diagnosis of obstruction. Deep peristaltic waves were observed progressing downward into the left lower quadrant. We made a diagnosis of obstruction, probably atresia, located high in the small bowel and advised immediate operation. Circumstances did not permit operation until twenty-four hours later. In the interim, a flat film disclosed two large, confluent air bubbles of the abdomen (Fig. 5). These were of about equal size and were correctly interpreted by the roentgenologist to represent the stomach and duodenum. After passing a catheter into the stomach, they disappeared. A subsequent film revealed no air at all in the abdomen, sealing the diagnosis of atresia of the bowel (Fig. 6).

At operation, the duodenum presented itself equal in size to the stomach. The pylorus could not be identified. The obstruction was located in the third portion of the duodenum near the ligament of Treitz; it was not dissected out. An anastomosis between the duodenum and jejunum was made. Postoperative course was stormy. The baby left the hospital after four weeks, having regained his birth weight.

At the age of 4 months the infant appeared to be perfectly normal. A complete gastrointestinal x-ray study at this time revealed that the duodenum had not completely



returned to normal size but was approximating it. A barium and milk mixture had not completely passed from the stomach at the end of three and a half hours, but it did pass from the stomach before the end of five hours. The infant stomach should empty itself of a barium and milk mixture within three hours. Prior to 4 months of age, this child's gastrointestinal tract had become adequate for his physiologic needs. However, anatomically it had not completely readjusted itself.



Fig. 6.—Case 3. Roentgen-ray film after escape of gas from stomach and duodenum. Note there is no gas in the entire gastrointestinal tract.

CASE 4.—Baby Mi. was a full-term infant, born Aug. 12, 1945, at St. Luke's Hospital, Chicago. The pediatric resident was called thirty hours after birth on account of persistent vomiting and marked abdominal distention. Visible peristalsis was absent and the abdomen was silent. Dr. S. C. Henn made a diagnosis of bowel obstruction with peritonitis thirty-eight hours after birth. Eight hours later celiotomy was performed. The abdomen was filled with air and meconium. The small bowel was adherent to the anterior abdominal wall, where there were two perforations. Adhesions were fibrous, necessitating sharp dissection from the anterior peritoneum, liver, stomach, and gall bladder. This process had evidently been going on in utero for a considerable time. After the bowel was freed, the mechanism could be identified, and was found to consist of a cord atresia of the ileum, 3 cm. above the ileocecal junction, and a defect in the mesentery through which the terminal ileum had herniated. It had then rotated counterclockwise, having made two complete turns. There was a third perforation, this one of the terminal portion of the ileum. Here the ileum was firmly bound to the posterior peritoneum, which was also perforated, and the retroperitoneal space was filled with meconium. The serosa of all of the involved bowel was dull. There were numerous areas of threatened perforation. This damaged portion of the bowel (Fig. 7), when resected, measured 53 cm. A side-to-side ileocecostomy was performed. Toilet of the abdominal cavity and retroperitoneal space was done by aspiration. The abdominal wall was closed in layers with interrupted, chromic

catgut and silk. Cultures showed a light growth of colon bacilli at the end of twenty-four hours. Penicillin was administered postoperatively. The wound healed by primary union.

*Postoperative Course.*—The bowels moved on the fourth day. Water was given by mouth for the first time on the third day, and formula on the fourth. Weight on the fourth day was 8 pounds, 5 ounces. The abdomen began to distend during the second week postoperatively and the stools became frequent and fatty. By the fifth week, the weight was 9 pounds, 1 ounce. At this time the baby became acutely ill, the temperature rising to 102° F. The stools became watery and frequent, up to twenty a day. Stool cultures revealed organisms of the salmonella group. Sulfaguanidine and penicillin were administered. The temperature returned to normal and the stools became much less frequent,

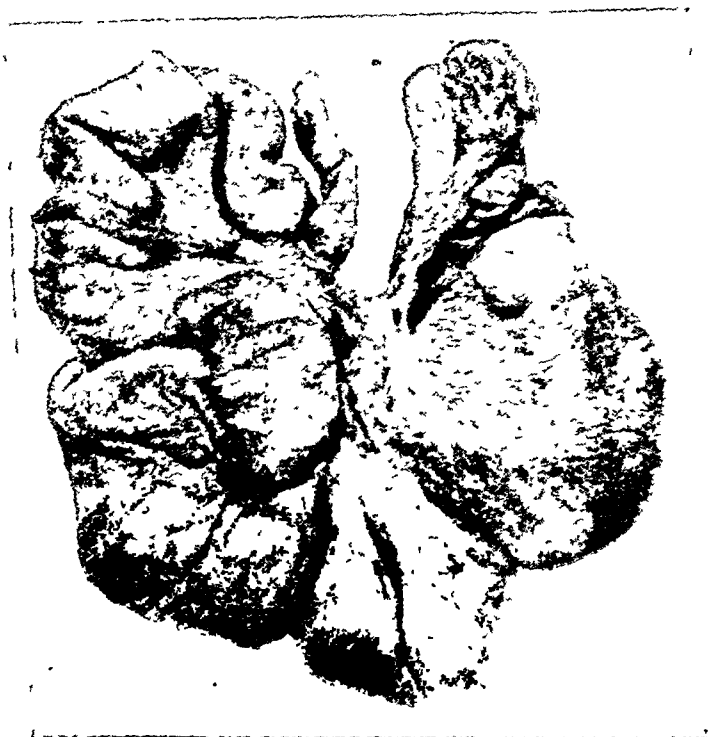


Fig. 7.—Case 4. Resected portion of ileum. Note hypertrophy and distention.

averaging three or four a day, but the weight continued downward to 7 pounds by the ninth week of life (Fig. 8). Although death seemed inevitable, we started the baby on a concentrated pancreatic extract, 0.5 Gm. three times daily. The weight increased, stools became more normal, and the abdominal distention receded. He began to take note of his surroundings. His vigor greatly improved. When 108 days old, the baby weighed 10 pounds, 7 ounces, and appeared to be on the way to recovery. At this time, an epidemic of upper respiratory virus infection broke out on the children's floor. This baby, the second one of five to die, began to cough on the one hundred twelfth day of life. The temperature rose to 104° F., the abdomen again became distended, and the baby died on the one hundred fifteenth day of life.

*Necropsy.*—Cause of death was bronchopneumonia and inanition. There were passive congestion and bronchopneumonia of the lower lobes of both lungs, moderate fatty change of the liver, distention of the stomach, ileum, and the colon, and a well healed ileocolostomy measuring 12 cm. in diameter (Fig. 9). The small bowel from the ligamentum of Treitz to the ileocolostomy measured 220 cm. There was no obstruction of the gastrointestinal tract. The pancreas was normal.

CASE 5.—Baby Ma., a Negro male infant weighing eight pounds, eight ounces, was born by cesarean section of a diabetic mother at St. Luke's Hospital, Chicago, and transferred to the pediatric service 7:30 P.M., April 18, 1946, forty-three hours after birth, on account of frequent vomiting. The vomitus was bile stained. The baby had not retained a feeding since birth. It had passed nothing but meconium and a little blood-tinged mucus per ano.

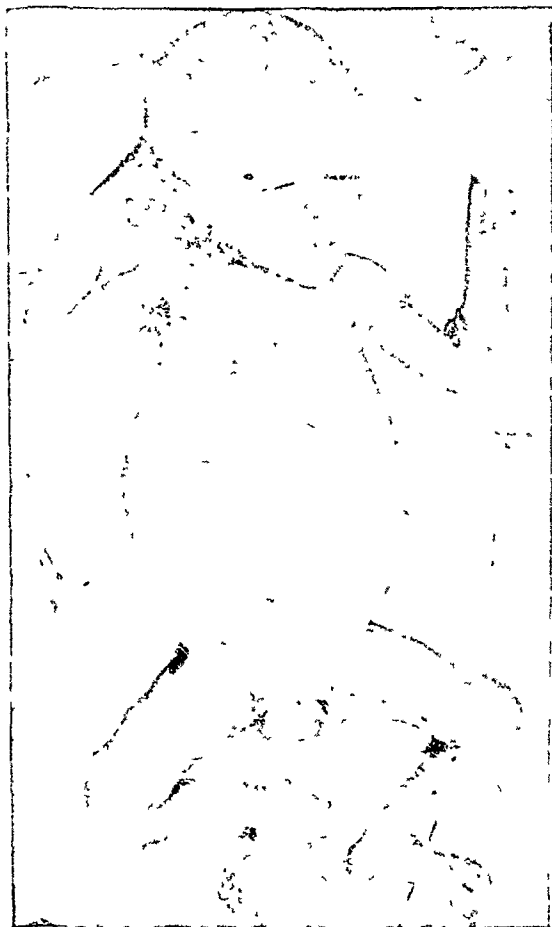


Fig. 8.—Case 4. Photograph of baby at lowest ebb. Note cellac-like appearance.

The abdomen was greatly distended and bowel sounds were present. Visible peristalsis was not present. A barium enema on admission to pediatrics revealed that the lower bowel was patent up to the cecum. Absence of large gas bubbles on a flat plate spoke against atresia. Gas distributed through both the large and small bowel also spoke against complete obstruction. A thin barium mixture given per os the next morning showed that the obstruction was not complete, but the baby continued to distend and retained nothing by mouth. The infant had been receiving subcutaneous fluids. After surgical consultation with Dr. Foster McMillan, operation was planned while the patient was still in good condition. The operation was performed seventy-three hours after birth.

A greatly distended hyperemic ileum without inflammatory signs bulged from the incision. It was four times the normal size. The colon had largely rotated, but descent

was incomplete. The caput coli lay at the level of the umbilicus, angulated laterally at a 90° angle, and was bound by a fibrous band. This and other fibrous strands to the posterior abdominal wall constricted the head of the cecum and the terminal ileum enough to cause almost complete obstruction. When the bowel was freed the ileum decompressed itself into the cecum, which was then brought into normal position and fixed.

*Postoperative Course.*—During the first, second, and third day, the baby progressed well without abdominal distention or regurgitation. Food was retained and the bowels moved. On the fourth day signs of skin infection about the wound as well as on other parts of the body appeared. The wound suppurated and the skin sutures sloughed out. The wound was supported by adhesive bridges.



Fig. 9.—Case 4. Autopsy specimen showing ostomy between ileum and cecum.

The baby gained ground slowly. He retained most of his feedings but regurgitated some each day. The day before operation he weighed 8 pounds, 4 ounces. Ten days later he weighed 7 pounds, 13 ounces. At the end of four weeks he had regained his birth weight. During the subsequent five weeks he gained another pound. At this time he stopped regurgitating, began to gain rapidly, and was discharged ten weeks after birth, weighing 9 pounds, 10 ounces. By this time the wound was completely healed. Penicillin was the chief anti infection drug used.

#### SUMMARY

We have presented the salient features of five cases of intestinal obstruction of the newborn, three of atresia and two of extrinsic obstruction. Two

cases of demonstrated atresia had other defects which necessitated the resection of large portions of the ileum, 118 cm. in Case 2 and 55 cm. in Case 4.

These two cases deserve special consideration. Each patient survived the immediate effect of the operation but developed a celiac-like syndrome. Case 2, having lost 118 cm. of small bowel, developed a greatly distended abdomen and passed fatty stools for several weeks. Later, the stools lost their fat and the abdomen adjusted toward the normal. Nevertheless the baby died of inanition on the one hundred twelfth day of life. The same syndrome developed in Case 4 after resection of 55 cm. of ileum. The baby appeared to be approaching its demise when concentrated pancreatin, well diluted in the formula, rapidly changed the picture. He then appeared to be on the road to recovery, when he was carried off by an epidemic of severe respiratory infection which took four other babies in the same nursery.

Arnheim<sup>2</sup> reported a patient who developed a similar syndrome after resection of 23 cm. of ileum. He found pancreatin helpful in a successful but long drawn out struggle.

These clinical facts, coupled with the autopsy findings in Cases 2 and 4 and the postoperative x-ray findings in Case 3, indicate that the young bowel has a remarkable compensatory ability. The large lumen above the atresia and the small lumen below tend to equalize each other, and the shortened bowel grows rapidly in length. Linear growth is a normal function of the infant bowel, and apparently the rate of growth is accelerated in the shortened bowel.

It is suggested, therefore, in cases of massive resection, that every effort be made to keep these babies alive until the compensatory factors accomplish their goal. Pancreatin is a material aid. We wish to emphasize the following facts:

1. The pediatrician does not usually see babies with congenital bowel obstruction until the third day of life.
2. The cardinal symptoms are persistent, nonprojectile, bile-stained vomiting, abdominal distention, and visible peristaltic waves.
3. Roentgen-ray films are helpful, but barium sulfate by mouth is unnecessary. It is usually harmful and wastes precious time.
4. The necessity for early operation cannot be overemphasized.
5. Ladd demonstrated the value of establishing continuity of the lumen by side-to-side anastomosis.

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## GENERAL ANESTHESIA IN THE DIFFICULT PEDODONTIC PATIENT

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THE purpose of this work is to develop a technique of anesthesia which would make possible the accomplishment of extensive dental operations for children without physical pain or psychic trauma. The dental profession has been engrossed primarily with the mechanics of its work to the extent that the psychic effects of dental treatment have been largely overlooked. With some children this condition has produced unfortunate results. Almost without exception a child who requires early dental attention will be a dental patient all of his life. As a young adult it becomes his prerogative and his responsibility to seek regular dental care. Whether or not he does so will depend to a large extent upon the attitudes he has developed during his childhood experience. It is a part of our professional responsibility to society to make the relationship between the profession and society as pleasant as possible.

The advancement in surgery has been correlated with the progress in the science of anesthesia. The immediate problem in successfully managing difficult child patients is to find some technique of anesthesia which would permit the dental operator to work carefully and successfully in the mouth. The psychic trauma would be reduced to a minimum, and the operator could devote his whole attention to the treatment. He could accomplish work of a nature impossible on a conscious patient, and could do an amount of work at one time which would ordinarily require many visits to a dental office.

It is important to avoid frightening a child, who, after 2 years of age, will carry the unpleasant experience and fear to later life.<sup>1</sup> Children under 5 years of age are too young to understand explanation, and it is desirable to have sufficient sedation to produce amnesia and reduce strain and fatigue for the period immediately preceding operative manipulations. In certain terror-struck and excited children, a basal narcosis by the oral or rectal route while the patient is in his own room avoids commotion and disturbance enroute to the operating room.

Differences of resistance to anesthesia are largely differences in metabolic state.<sup>2</sup> The level of metabolic rate represents the degree of reflex irritability and oxygen demand. Metabolic levels are higher in children between the ages of 2 and 12 than at any other time in the life cycle (Chart 1). During this period, the pain thresholds are lowered and the addition of apprehension and fear increases the metabolic rate. Sedation by drugs is effective in increasing the threshold to pain and lowering the metabolism by allaying excitement, thus reducing the amount of oxygen required, and the period of restlessness and

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excitement which frequently accompanies the return to consciousness from anesthesia can be largely circumvented.

Basal anesthesia is a light degree of anesthesia obtained by giving sufficient preliminary medication. It allows the patient to be brought to the operating room in an unconscious state, yet not sufficiently depressed for surgical procedure. In general, none of the nonvolatile agents should be used to depress the patient beyond basal narcosis into complete surgical anesthesia. Local anesthesia might be used as an adjuvant, or a final leveling off to the necessary depression can be conducted by one of the volatile or gaseous agents.<sup>3</sup> Tribromethanol in amylene hydrate (Avertin) has prevailed over other hypnotics as a basal agent. The barbiturates possess some advantages as central nervous system depressants; any degree of depression from slightest sedation to surgical anesthesia can be obtained by selection of drug, dose, and route of administration, and they have the unique property of affording protection against the toxic effects of local anesthetics.

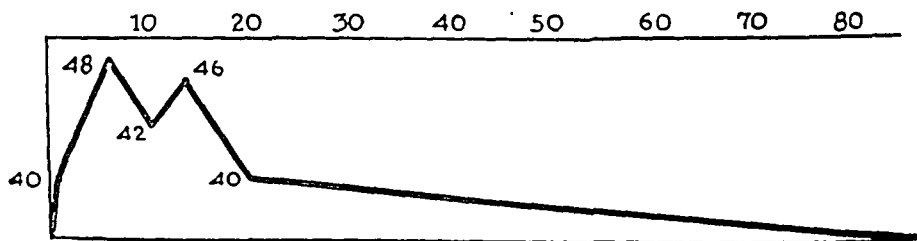


Chart 1.—Curve of normal metabolic rate through life, estimated in calories per hour per square meter of body surface. The curve of oxygen demand and reflex irritability was parallel.

#### METHOD

Two kinds of patients were selected for the work to be done: children who would not cooperate while in a conscious state; and those small children whose mouths were extensively in poor condition, necessitating painful procedures and repeated visits to the dentist's office. Forty-two children were studied for this report. Nineteen were male. The age range was from 2 to 13 years. The physical state was good in all cases, the entire group being placed in Group I, in accordance with the American Anesthesia Society standard of risking patients.

*Group I.*—Tribromethanol (avertin) was the basal agent chosen in eleven cases. Avertin fluid, 120 mg. per kilogram of body weight, was prepared as a 2½ per cent solution in distilled water, and 60 mg. of the total dose were instilled rectally in the patient's room thirty minutes before the scheduled surgery time. Every five minutes, 10 mg. doses were added until unconsciousness was obtained. Thus, the phlegmatic or hypothyroid type of patient needed only 60 or 70 mg. to give sufficient basal narcosis, while the wiry, active patient required the full 120 mg. dose. As soon as the basal sedation was reached, atropine sulfate, in a dose related to size and vigor of the patient, was administered subcutaneously, the child was removed to the operating room, and endotracheal intubation performed under direct laryngoscopy by the oral or nasal route. Narcosis was satis-

factory in 100 per cent of the patients, the children arriving to the surgical amphitheater unconscious, and flushed, with respirations quiet but adequate and pulses within normal range. Induction of general anesthesia was rapid, smooth, and unattended by excitement. The emergence time varied from four to eleven hours, averaged five and one-half hours, and was complicated by nausea and vomiting in 30 per cent. Restlessness during the awakening period was minimal. The emergence time was tentatively considered that period from the administration of the avertin medication to the first postoperative waking responses of movement and return of reflexes.

*Group II.*—Although tribromethanol (avertin) produced a satisfactory basal anesthesia, it presented the troublesome disadvantages of a long preliminary preparation. For this reason, sodium propyl-methyl-carbinyl allyl barbiturate (Seconal),\* a short-acting barbiturate, was chosen for trial, because of its quick action and its relatively short duration.<sup>4</sup> It differs from barbital and phenobarbital in being detoxified and oxidized within the body with great rapidity, rather than being excreted in the urine. The sedative effect of seconal is quite unique in that there are few depressive symptoms demonstrated six to ten hours after administration of the drug.<sup>5</sup> Its therapeutic index is greater than other common soluble barbiturates; larger doses can be given to obtain dramatic but safe sedation. It is very rapidly absorbed when given by mouth or by rectum. Oral administration was employed when feasible. Its rapid action was only slightly retarded when administered by the rectal route, which was used for small children or infants who could not swallow capsules. The pierced capsule was inserted in the manner of a suppository, the powder suspended in 5 c.c. of tap water and injected by rectal catheter. An additional 2 to 3 c.c. of water was given to assure the patient's receiving the full dose. The buttocks were then taped to prevent expulsion. Maximal analgesia was obtained in thirty to sixty minutes, but the action persisted for several hours.

The basis for estimating dosage was the age and weight of the patient, but consideration was given to the child's general condition, body build and vigor, and nervous reactivity.<sup>6</sup> Individual doses were increased above Breslow and Poncher's<sup>7</sup> recommended dose of 0.1 grain (6.5 mg.) per pound of body weight to a calculated dose of 0.14 to 0.15 grain (9 to 9.5 mg.) per pound. A group of nine patients received this heavy seconal medication administered orally or rectally. Atropine sulfate was given in addition to the seconal to prevent increased secretions. Narcosis was excellent, unconsciousness occurring in ten to twenty minutes in all cases; the patients were flushed, had adequate respiratory exchange, and responded only slightly, if at all, to painful stimulation. However, the time of the awakening was retarded, and considerable restlessness was observed. The length of time from administration of seconal to emergence varied from two and one-half to fifteen hours and averaged seven hours. In order to reduce the duration of narcosis, d-Desoxyephedrine hydrochloride, in a dosage of 1 mg. per fifteen pounds of body weight, was given to six patients. The combination of this drug and seconal seemed to enhance the postoperative

\*Seconal is a preparation manufactured by Eli Lilly & Company.



restlessness, which led to its discontinuance. These six cases were considered too few to determine if the emergence time was decreased by the administration of the analeptic.

*Group III.*—Demerol is reported to have the drying action of atropine and the analgesic action of morphine without its respiratory depressant effect. Twenty-two patients were given a combination of seconal and atropine, with the object of reducing the seconal dosage, and, by means of this balanced combination, producing adequate sedation and drying of secretions. These patients, 2 to 10 years of age, were given .05 grains (3 mg.) of seconal per pound body weight, to a maximum total dose of 3 grains, followed by a hypodermic injection of demerol and atropine sulfate.

TABLE I. TABLE OF PREANESTHETIC MEDICATION—SECONAL, DEMEROL, AND ATROPINE\*

AGE (YR.)	WEIGHT (LB.)	SECONAL† 1½ HR. PREOPERATIVELY (GRAINS)	DEMOROL AND ATROPINE HYPO. 1 HR. PREOPERATIVELY		ATROPINE ALONE HYPO. 1 HR. PREOPERATIVELY (MG.)
			DEMOROL (MG.)	ATROPINE (MG.)	
Under ½	12-15	¾	—	—	—
½-1	Under 21	1	—	—	—
1 & 2	21-30	1½	10	0.65	0.13
3 & 4	31-38	2	15	0.08	0.16
5 & 6	39-46	2½	15	0.11	0.19
7 & 8	47-55	2¾	20	0.13	0.21
9 & 10	56-63	3	25	0.16	0.32
11 & 12	64-78	3	25	0.19	0.48
13 & 14	79-100	3	35	0.21	0.48
15 & 16	100-120	3	50	0.32	0.48
17 & 18	120-140	3	75	0.48	0.48
Over 18	140-160	3	75	0.48	0.48

\*The above table presents maximum dose for healthy, normal children. Reduced doses are indicated for debilitated, cachetic, or actually ill patients.

†This total amount of seconal is to be given in divided doses; the first half, one and one-third hours before surgery; the second half, twenty minutes later, if the patient shows no undue sensitivity.

Table I illustrates the range of demerol, seconal, and atropine dosages used in Group III. The response to the medication was singularly satisfactory, though the depth of narcosis was not so great as that in the first two groups. The patients were sleeping lightly, and responded when moved or stimulated. The induction of anesthesia was smooth and unattended with coughing, excitement, or increased secretions. Emergence within an average of four hours was quiet and unaccompanied by restlessness. The incidence of nausea and vomiting seemed about the same as in the second (seconal-atropine) group of cases. Blood pressure readings showed no demonstrable change from those made prior to medication. These patients were in a sufficiently light state of narcosis to retain their cough reflexes. On questioning, none of them was able to recall the trip to the operating room.

#### TECHNIQUE OF ANESTHESIA AND DENTAL SURGERY

The technique of anesthesia in forty of the forty-two patients was the orotracheal or nasotracheal insufflation of ether. A wet gauze pack placed lightly in the pharynx around the tube safeguarded against aspiration of tooth particles,

cement, blood, and other debris. A 21-26 French gauge Magill catheter was used, and all intubations were affected by direct laryngoscopy. An angular finger valve (Figs. 1, 2, and 3) connected the endotracheal catheter to the ether-air insufflation apparatus (Beck-Mueller or Richardson). A Y piece in the inlet hose permitted the addition of oxygen when necessary. One patient was given Vinethene alone; another had the dental work completed in its entirety under the heavy secondal medication.

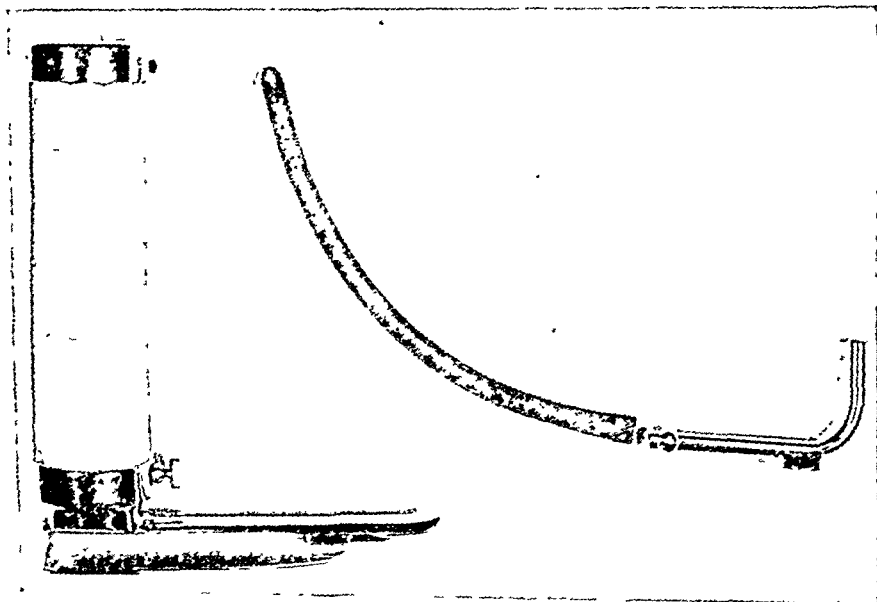


Fig. 1.—Laryngoscope with child blade, Magill endotracheal tube, and angular finger valve.

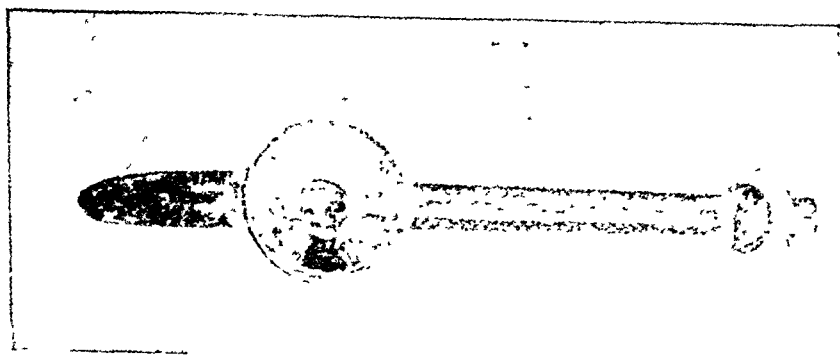


Fig. 2.—Close-up of angular finger valve showing outlet for exhalation.

The supine position, which was used in all cases, did not seem to hinder the performance of the dental surgery. Care was exercised to prevent the aspiration of foreign particles. The restorative work in many cases was very extensive, necessitating forty to one hundred twenty minutes for completion of the

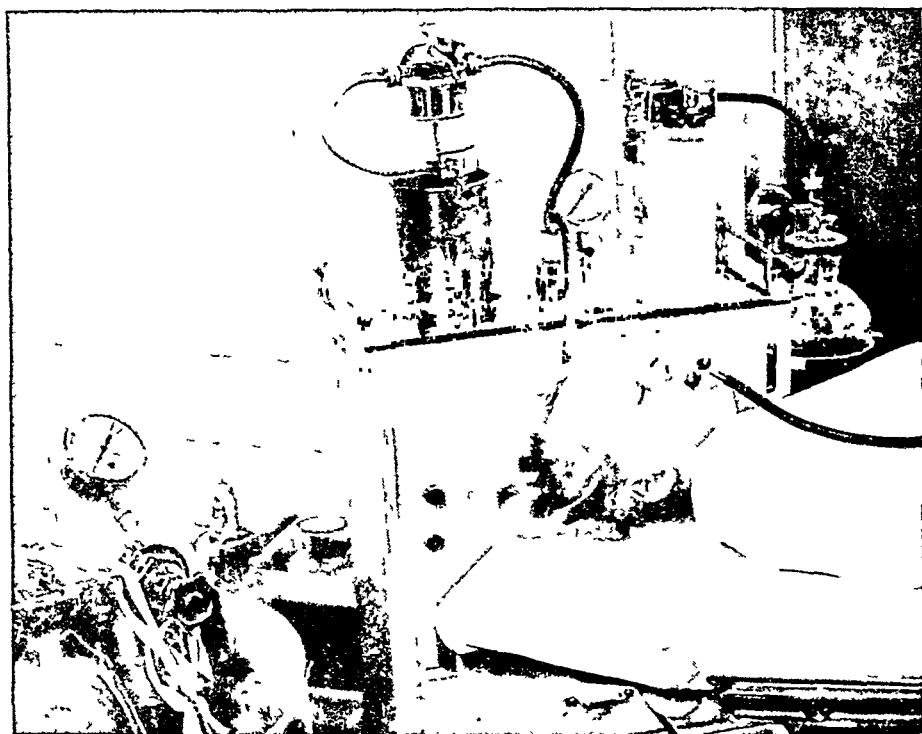


Fig. 3.—Patient anesthetized with methene and ether, intubated, and ready for dental repair task. The shortest surgical procedure took fifteen minutes; the longest, one hundred twenty minutes; the average surgical time was fifty-one minutes

The dental work included the extraction of teeth, the restoration of carious teeth in cement and in silver amalgam, treatments with Thymol Iodide and with silver nitrate. No drilling was done in any case because of the explosion hazards of ether. However, it was felt that the probability of explosion was so slight with the use of insufflation ether-air, that the drilling of teeth could be safely used in the future, particularly if the foot-driven drill were used.

TABLE II. SUMMARY OF CASES

GROUP	I.	II.	III.
DRUGS	Tribromethanol (60 to 120 mg. per kg. body weight) and atropine	Seconal (0.14 to 0.15 grains per lb.), and atropine	Seconal (0.05 grains per lb.), demerol (10 to 25 mg.), and atropine
NO. OF CASES	11	9	22
EMERGENCE*	4 to 11 hours (average 5½ hours)	2½ to 15 hours (average, 7 hours)	2 to 7 hours (average, 4 hours)
EFFECTS OF MEDICATION	100% unconscious	100% unconscious	100% unconscious
RESTLESSNESS	++	+++	+
NAUSEA AND VOMITING	+	+	+

\*From administration of medication to first response (movement and return of reflexes).

+ Minimal or insignificant.

++ Troublesome

+++ Severe.

## COMMENTS

In three groups involving forty-two patients (Table II), an attempt has been made to develop a safe and satisfactory technique for the preoperative sedation of the pedodontia cases. Basal narcosis has been the goal for the young child who was not to be reasoned with. However, patients 8 to 10 years old could for the most part understand the situation and cooperate. Therefore, medication was decreased at these age levels to produce sedation only.

Two hazards have been considered throughout this work. The first is the danger of respiratory obstruction after medication and prior to arrival in the operating room. The second is the danger of sensitivity to the drugs used, particularly to the barbiturates. In order to decrease the former, the reduced doses of the rapid acting drug, seconal, were used. There has been no occurrence of sensitivity in the forty-two cases herein reported and in an additional sixty patients other than dental medicated with seconal. In order to lessen the hazard of idiosyncrasy, the total seconal dose was divided into two equal parts and the second part given twenty minutes after the first. This technique was used in the last fifteen patients of the third group, and it is planned to continue it in the future.

Barbiturates present the disadvantages of variability of response and accumulation of effect, thus causing emergence from the fast-acting drugs to assume similar action to that of the long-acting drugs. It is conjectured that an analeptic agent such as d-Desoxyephedrine hydrochloride may reduce the recovery period and make the barbiturate approach more ideal.

## SUMMARY

1. The psychic trauma to a child undergoing dental repair has been overlooked by many of us; studies are presented in the use of basal narcosis and general anesthesia for extensive pedodontia in forty-two patients.
2. Favor is given to the preoperative sedation of seconal in combination with demerol and atropine, followed by endotracheal insufflation of ether.

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## Case Reports

### REACTION IN TIBIA FOLLOWING INTRAMEDULLARY ADMINISTRATION OF FLUIDS

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FOR a number of years sternal puncture has been an accepted and approved method for obtaining bone marrow specimens for examinations in suspected blood dyscrasias. In 1940 the intramedullary route was proposed as an avenue for the administration of parenteral fluids, including glucose, plasma, and blood. Tocantins described this method in a preliminary report which appeared in 1940,<sup>1, 2</sup> and in subsequent papers appearing in the *Journal of the American Medical Association*,<sup>3</sup> and in the *Annals of Surgery*.<sup>4</sup>

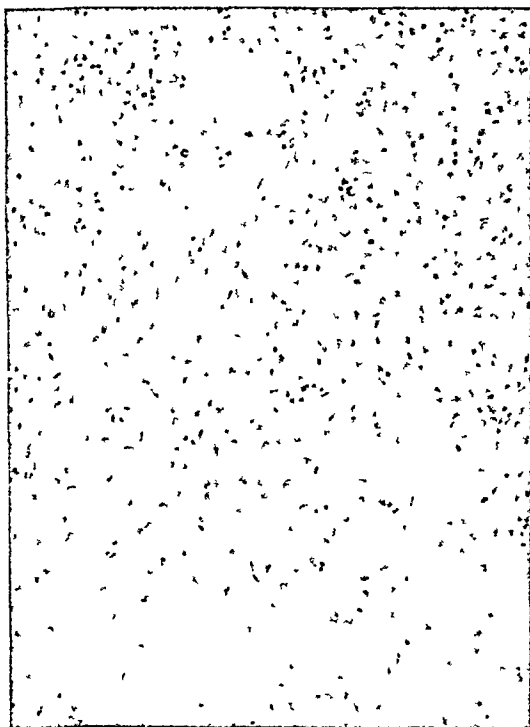


Fig. 1.—The photomicrograph shows necrosis and the presence of atypical giant cells with round cell infiltration.

The following case is reported because it showed an unusual complication and because the histologic picture simulated tuberculosis.

The patient was a 3-year-old, acutely ill girl, operated upon on June 13, 1945, for acute appendicitis with diffuse peritonitis. During the immediate post-operative period the venous route proved inadequate for administration of the

necessary fluids, and the intramedullary method was chosen. A needle was inserted into the marrow cavity of the left tibia and later another needle into the right tibia through which glucose in saline, plasma, citrated blood, and penicillin were administered. The child was discharged from the hospital on the fourteenth postoperative day. At this time the needle site over each tibia was well healed. These had been dressed with sulfanilamide powder and sterile gauze following the removal of the needles.



Fig. 2.—X-ray film of the tibia made fourteen weeks after onset of illness shows irregular destruction of the shaft with new periosteal bone production.

Culture of the peritoneal fluid taken at the time of operation showed no growth. Pathologic report of the removed appendix was "acute suppurative appendicitis."

On July 23, 1945, a painful, tender, fluctuant swelling appeared over the left tibia at the site of the previous infusion. An x-ray film of the left leg was reported negative. The mass was incised, and approximately 10 c.c. of thick,

creamy pus was evacuated from an abscess in the subcutaneous tissue. Healing was satisfactory.

On Sept. 13, 1945, she was brought into the office with a slightly tender, firm, nonfluctuant swelling of the left leg about one inch above the previous abscess. A tentative diagnosis of osteomyelitis was made, which was confirmed by x-ray examination. Films of July 23, 1945, were reviewed and revealed an area of rarefaction at the upper part of the left tibia in the metaphyseal region. The upper pole of the rarefaction was one inch below the epiphysal line. The new x-ray film of September 13, 1945, showed extension of this area of rarefaction. She was hospitalized and conservative treatment consisting of rest, high-caloric and high-vitamin intake was instituted. Penicillin was given intramuscularly in doses of 20,000 units every four hours. She was discharged from the hospital on Oct. 5, 1945. During her hospital stay her temperature never rose above 100° F.

Check-up x-ray examinations on Sept. 25, 1945, and Oct. 23, 1945, showed no essential changes in the pathologic process. X-ray films made on Nov. 25, 1945, showed that the area of rarefaction had progressed upward so that it was within one-half inch of the upper epiphysal plate with sclerosis about the upper and lower poles and with new periosteal bone production generally about this fusiform swelling.

Surgical intervention was deemed advisable. Saucerization of the involved portion of the tibia was performed on Dec. 11, 1945. One-half ounce of thick pus was evacuated from the marrow cavity of the bone. The abscess cavity was found to be lined with granulation tissue which also was plugging the cloaca through the cortical portion of the tibia.

The postoperative course was uneventful. There has been complete healing of the wound, and check-up x-ray films reveal the absence of active infection and complete filling in of the saucerized bone.

Microscopic section of the granulation tissue reported by Dr. A. A. Eggston showed numerous lymphocytes, plasma cells, and fibroblasts. There were some areas of necrosis and a few multinucleated giant cells. There was evidence of reticulo-endothelial hyperplasia and a slight tendency to cellular arrangement into tubercle-like areas. The diagnosis was chronic osteomyelitis, suggestive of tuberculosis. A number of the sections were stained for tubercle bacilli, but none could be demonstrated.

#### CONCLUSION

This method for the administration of fluids is of great value when other routes are not feasible, and this possible complication should not detract from its use as a life-saving measure when indicated.

The histologic appearance of the granulation tissue resembled tuberculosis, but careful examination of the sections failed to reveal the presence of tubercle bacilli. The postoperative course of the patient rules out tuberculosis.

Clinically, the reaction simulated a pyogenic osteomyelitis, but the negative cultures from the pus in the abdomen and in the tibia suggest that the infection was not of the ordinary pyogenic type.

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## MENINGITIS COMPLICATING CEPHALHEMATOMA

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CEPHALHEMATOMA is generally considered to be an almost innocuous condition of the newborn state, running a self-limited course. Grulee and Sanford<sup>1</sup> state that infection is certainly extremely rare. In reviewing the literature we have been unable to find any published report of spontaneous secondary infection of a cephalhematoma leading to purulent meningitis. We therefore present such a case.

A male child was born at Lincoln Hospital on June 6, 1946, from the right occipitoanterior position by normal spontaneous delivery. Though a full-term infant and in good condition, he was admitted to the premature nursery because of a low birth weight of 5 pounds and 5 ounces. The child passed meconium, voided, and took his feedings well. A mass, 4 cm. in diameter, was noted overlying the left parietal bone and extending up to, but not crossing, the sagittal suture. This mass was tense and nonpulsating. A parietal cephalhematoma was diagnosed. On the fourth day of life the baby became mildly jaundiced. However, there was no evidence of blood dyscrasia. The child continued to take all feedings well and regained  $1\frac{1}{4}$  oz. of the initial 3 oz. weight loss. Mild edema of both thighs and buttocks was also observed at this time. The cephalhematoma remained stationary in size and the edema and icterus persisted. By the seventh day the infant had exceeded his birth weight by  $\frac{1}{4}$  oz. On this day the patient's temperature suddenly rose to  $101.4^{\circ}$  F. Physical examination revealed no abnormal findings other than those previously noted. Penicillin therapy was started, 5,000 units being given every three hours. By the following day the temperature had dropped to  $99.0^{\circ}$  F.; the baby seemed much improved. Two days later, on the tenth day of life, the temperature again became elevated to  $101.8^{\circ}$  F. and the child refused his feedings. Resort was made to feeding by gavage. The cephalhematoma did not change in size or consistency, but the edema and icterus both disappeared. The baby had three loose, yellow stools and several small hypodermoclyses were administered for some loss of skin turgor. Treatment with penicillin was continued on empirical grounds. Physical examination on this, the tenth day, showed the ears, nose, and throat to be normal; the lungs were clear to percussion and auscultation; abdominal palpation was negative; there was no bulging of the anterior or posterior fontanels; there were no pathologic reflexes; the cephalhematoma showed no change. Urine examination was negative. Diarrhea, however, persisted, and oral feedings were therefore discontinued temporarily. The patient was maintained by parenteral fluids for the following two days. By the thirteenth day the diarrhea had abated and an Alacta formula was started. On the fourteenth day the temperature was  $99.0^{\circ}$  F. and the administration of penicillin was stopped. The baby was then taking all oral feedings well. His condition remained improved until the eighteenth day, when the temperature suddenly rose to  $104.0^{\circ}$  F. The child became cyanotic, exhibited signs of marked respiratory distress, with infra-sternal and suprasternal retraction on inspiration, and appeared critically ill. Moist, inspiratory rales were present throughout both lung fields and tetanic convulsive movements of the face and arms were noted. Sulfadiazine was ordered and the penicillin was started again with 15,000 units as the three hourly dose. In case the convulsive disorder might be an expression of hypocalcemic

From the Pediatric Service of Dr. Harry S. Altman, Lincoln Hospital.



tetany, blood was withdrawn for a serum calcium level and 5 c.c. of a 10 per cent solution of calcium gluconate was administered intravenously without benefit. At this time no evidence of meningeal irritation such as bulging fontanels, nuchal rigidity, or positive Kernig's or Brudzinski's signs were elicited. The child continued to do poorly despite sulfadiazine, penicillin, and oxygen therapy, and expired six and one-half hours later.

Permission for necropsy was obtained. The anatomic diagnoses were: (1) meningitis, purulent; (2) cephalhematoma, left parietal region, secondarily infected; (3) bronchopneumonia, bilateral, confluent; and (4) fatty degeneration of the liver.

There was a somewhat fluctuant mass about 5 cm. in diameter in the left parietal region of the scalp. On incision, thick, sanguinopurulent material exuded from the mass. The abscess was well demarcated and extended down to the bone, the periosteum having been destroyed and the surface of the parietal bone presenting a shaggy, roughened appearance, with some thinning of the bone.

Upon opening the cranial cavity the base of the brain was found to be bathed in a yellow, purulent material. There were small, localized areas of pus underlying the meninges all over both hemispheres of the brain. There was edema of the cerebrum with some congestion of the small pial vessels. On the internal surface of the left parietal bone, approximately 1.5 cm. inferior to the site of the abscess, a purulent area was noted surrounding one of the dural veins. Just beneath this localization of pus there was a purulent exudate on the corresponding area of the brain.

The thoracic cavity was opened and the organs were found to be in normal position and relationship to each other. There was no free fluid in the pleural cavities. The lungs were of an orange-red color, firm and rubbery in consistency. There were small areas of petechial hemorrhage in the pleurae anteriorly. On section, the lungs were more or less consolidated. No frothy fluid exuded on pressure. There were no local areas of infarction. The lungs were of a homogeneous appearance. The trachea and bronchi were slightly edematous and congested. No mucus or obstructions were found in the lumina.

The liver was deep purple, but there were many areas of yellow discoloration on the anterior surface. The organ was firm in consistency. On section, it could be cut with ease and showed small areas of fatty degeneration. The spleen, adrenals, and kidneys were normal. The alimentary tract was normal throughout.

All media planted with material from the abscessed cephalhematoma and from the meninges yielded *Bacillus pyocyaneus* in pure culture.

#### COMMENT

We have presented a case of a newborn infant in whom a cephalhematoma became secondarily infected in the absence of any trauma and without interference by "needling" or any other procedure, and in whom the resulting abscess went on to burrow through the parietal bone, causing a purulent meningitis with fatal termination. The organism which was recovered from both the infected cephalhematoma and from the meninges was found to be *B. pyocyaneus* (*Pseudomonas pyocyanea*). Blood-borne infections by this organism are not rare in the neonatal state and frequently pursue a fulminating course.<sup>2</sup> The primary site of infection is described as usually being in the gastrointestinal tract, the umbilicus, or the skin.<sup>2</sup> Our case presented no evidence of infection of the skin or umbilicus, and we feel that it is not unreasonable to assume that our patient had a focus in the gastrointestinal tract which seeded the cephalhematoma by

way of the blood. Holt and McIntosh<sup>3</sup> state that following severe traumatism, cephalhematomata may go on to abscess formation and either open externally or burrow, but that this result is seldom seen.

Our case re-emphasizes the fact that meningitis may occur in the newborn without the classic signs and symptoms of the disease. It, therefore, is important that diagnostic lumbar puncture be done in that age group when there is unexplained sepsis.

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# American Academy of Pediatrics

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## Proceedings

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### REPORT OF THE MEETING OF THE EXECUTIVE BOARD OF THE AMERICAN ACADEMY OF PEDIATRICS

CHICAGO, ILL., NOV. 24, 25, 1946

A meeting of the Executive Board was held at the Palmer House, Chicago, on Sunday and Monday, November 24 and 25, 1946. The first session was called to order at 10 A.M., Sunday, by the President, Dr. Jay I. Durand. There were present Drs. Jay I. Durand, Lee Forrest Hill, Marshall C. Pease, Edgar E. Martmer, Oliver L. Stringfield, Paul W. Beaven, Warren W. Quillian, James W. Bruce, George F. Munns, Roger L. J. Kennedy, Vernon W. Spickard, Félix Hurtado, Joseph S. Wall, and Clifford G. Grulee.

The following applicants were elected to Fellowship:

#### *Region I*

George R. Alpert, New York, N. Y.  
Glidden Lantry Brooks, Lewiston, Maine  
Enid C. Brown, Buffalo, N. Y.  
Charles C. Chapple, Philadelphia, Pa.  
Martha L. Clifford, Hartford, Conn.  
David J. Cohen, Meriden, Conn.  
Henry Cohen, Brooklyn, N. Y.  
Joseph H. DiLeo, New York, N. Y.  
David Dragutsky, Brooklyn, N. Y.  
Herman Eisenberg, Washington, D. C.  
Henry M. Eisenoff, New York, N. Y.  
L. Stearns Fannin, Bradford, Pa.  
John L. Finnegan, Flushing, Long Island, N. Y.  
de la Broquerie Fortier, Quebec, Que.  
Irvin Fradkin, Freeport, Long Island, N. Y.  
Clarence F. Friedman, Brooklyn, N. Y.  
Martin J. Glynn, Jr., Rockville Centre, N. Y.  
Harold G. Grayzel, Brooklyn, N. Y.  
Martin Green, Atlantic City, N. J.  
Adelard Groulx, Montreal, Que.  
Ernest T. Heffer, Brooklyn, N. Y.  
Theodore G. Holzsager, Brooklyn, N. Y.  
Philip J. Kozinn, Brooklyn, N. Y.  
Alan Charles Levin, Brooklyn, N. Y.  
Leo Litter, Hartford, Conn.  
George W. McCormick, Staten Island, N. Y.  
Israel Miller, Brooklyn, N. Y.  
Ralph E. Moloshok, New York, N. Y.  
J. Leonard Moore, Princeton, N. J.  
Alexander S. Nadas, Greenfield, Mass.  
Benjamin Newman, Brooklyn, N. Y.  
Nolan A. Owens, Washington, D. C.

Alexander E. Rostler, Fall River, Mass.  
 Russell E. Sangston, Uniontown, Pa.  
 William A. Schonfeld, New York, N. Y.  
 Herbert Sherwin, Cambridge, Mass.  
 David W. Sherwood, Wellesley Hills, Mass.  
 Eleanor R. Stein, Harrisburg, Pa.  
 Stuart S. Stevenson, Fairfield, Conn.  
 Stewart C. Wagoner, Schenectady, N. Y.  
 Irving Weinstock, Brooklyn, N. Y.  
 Harry Wexler, Brooklyn, N. Y.  
 Herbert M. Williams, Kew Gardens, N. Y.  
 Benjamin J. Wood, Pittsburgh, Pa.

### *Region II*

Egbert V. Anderson, Pensacola, Fla.  
 Thomas Davis Dotterer, Columbia, S. C.  
 Don William Freeman, Denison, Texas  
 Edward Alun Harris, Fairfield, Ala.  
 Bernhard H. Hartman, Asheville, N. C.  
 Basil Bradbury Jones, Richmond, Va.  
 William White Kelton, Jr., Austin, Texas  
 David William Martin, West Palm Beach, Fla.  
 Eugenia Elizabeth Murphy, Arlington, Va.  
 Edwin Paul Scott, Louisville, Ky.  
 Amelia Burns Sheftall, Jacksonville, Fla.  
 Daniel Lesesne Smith, Jr., Spartanburg, S. C.  
 Edwin Robeson Watson, Macon, Ga.

### *Region III*

James H. Bahrenburg, Canton, Ohio  
 J. Joseph Baratz, Chicago, Ill.  
 Richard Winston Blumberg, Cincinnati, Ohio  
 Mary S. Boyden, Lawrence, Kan.  
 Lyman Ray Critchfield, St. Paul, Minn.  
 John C. Danahy, Cincinnati, Ohio  
 David Richard Davis, Emporia, Kan.  
 Vernon Richard DeYoung, Chicago, Ill.  
 Mark Wendell Dick, Grand Rapids, Mich.  
 Katherine Dodd, Cincinnati, Ohio  
 William H. Eberle, Ashtabula, Ohio  
 Harry L. Faulkner, Chicago, Ill.  
 Joseph Henry Garthe, Rockford, Ill.  
 Kurt Glaser, Chicago, Ill.  
 William H. Gronemeyer, Lakewood, Ohio  
 Lloyd E. Harris, La Fayette, Ind.  
 Robert D. Hart, Peoria, Ill.  
 Manes S. Hecht, Detroit, Mich.  
 Oliver William Hosterman, Columbus, Ohio  
 Gertrude E. Howe, Chicago, Ill.  
 Robert L. Jackson, Iowa City, Iowa  
 F. Craig Johnson, Denver, Colo.  
 George John Klok, Council Bluffs, Iowa  
 Hyde S. Leland, Detroit, Mich.  
 Sol Loude, St. Louis, Mo.

Emerson K. McVey, Chicago, Ill.  
 Frederick J. Margolis, Kalamazoo, Mich.  
 Irving B. Richter, Chicago, Ill.  
 John Richard Schroder, Janesville, Wis.  
 Charles L. Steinberg, St. Paul, Minn.  
 Carl F. Wagner, Cincinnati, Ohio  
 Paul V. Woolley, Jr., Detroit, Mich.  
 Melvin Francis Yeip, Cleveland, Ohio  
 Ruth M. Kraft, Detroit, Mich.

#### *Region IV*

Leo S. Bell, San Mateo, Calif.  
 Sherod M. Billington, Seattle, Wash.  
 Edward Campion, San Rafael, Calif.  
 Charles H. Cutler, San Francisco, Calif.  
 Richard D. Cutter, Palo Alto, Calif.  
 Lucas W. Empey, Sacramento, Calif.  
 Scott H. Goodnight, Portland, Oregon  
 Percy F. Guy, Seattle, Wash.  
 Archie F. Hardymont, Calgary, Alta., Can.  
 Barbara Hewell, Honolulu, T. H.  
 George D. Husser, Richmond, Calif.  
 William M. Petty, Santa Maria, Calif.  
 George O. Prieur, Calgary, Alta., Can.  
 Saul J. Robinson, San Francisco, Calif.  
 Vincent Rounds, Los Angeles, Calif.  
 Mandel L. Spivek, Beverly Hills, Calif.  
 Robert A. Tidwell, Seattle, Wash.  
 Homer T. Clay, Tacoma, Wash.  
 Peter Cohen, San Francisco, Calif.  
 David M. Goldstein, Los Angeles, Calif.  
 Edward A. Loeb, Fontana, Calif.  
 Stanley Louie, San Francisco, Calif.

#### *Region V*

Paulo de Barros Franca São Paulo, Brazil  
 José de Magalhães Carvalho, Rio de Janeiro, Brazil  
 Odilon de Andrade Filho, Rio de Janeiro, Brazil  
 Estella Budiansky, Porto Alegre, Rio Grande do Sul, Brazil  
 Roberto Berro, Montevideo, Uruguay  
 Bolívar Delgado Correa, Montevideo, Uruguay  
 María Luisa Saldún de Rodríguez, Montevideo, Uruguay  
 Upon application the following were granted Emeritus Memberships:  
 Iris M. Chamberlain, Chicago, Ill. (Guatemala)  
 Elmer G. Horton, Columbus, Ohio  
 Frederick H. Meichner, Long Island City, N. Y.  
 E. C. Mitchell, Memphis, Tenn.  
 H. L. Moon, White Salmon, Wash.  
 J. Phillips Stout, Jersey City, N. J.  
 Henry Washeim, Jr., Utica, N. Y.

The resignations of Dr. Henry N. Pratt, New York City, Dr. Susan P. Souther, Columbus, Ohio, and Dr. Norman Nixon, Laguna Beach, Calif., were accepted.

Dr. M. Scherzer, Montréal, Que., was reinstated at his request.

Dr. Luis Siri, Argentina, was voted to Associate Membership upon recommendation of Dr. Félix Hurtado.

The following were given leaves of absence: Dr. Leo Batell, Durham, Conn., Dr. Marion S. Morse, Endicott, N. York., and Dr. Raymond H. Somers, San Jose, Calif.

### Report of Region I

This will probably be the last report from Region I as it is now constituted. The Academy's Study of Child Health Services has been the main activity throughout our region. Through the efforts of our state chairmen, our region was the first to have all our states organized with executive secretaries and offices. One of our states was first, exclusive of North Carolina, to have all our questionnaires distributed. For these accomplishments we wish to thank the state chairmen: Drs. Foster of Maine, Stewart of New Hampshire, Clark of Vermont, Baty of Massachusetts, Root of Connecticut, Orr and Wilke of New York, Murray of New Jersey, Gilmartin and Barba of Pennsylvania, Handy of Delaware, Wharton Smith of Maryland, and Copeland of Washington.

At a meeting of the state chairmen, October 1, we were instructed to report their following unanimous opinions:

1. That a representative committee be established to interpret the findings of the Study of Child Health Services and make recommendations and policies to the Executive Board.
2. That it is their recommendation that the members of the Academy support the proposed meeting of the Fifth International Congress when it is held. They further unanimously voted that due to unsettled conditions in this country, Europe and Asia, the holding of the Fifth International Congress in July, 1947, as proposed, is premature and should be postponed.
3. They specifically directed us to express their thanks and appreciation to the Committee in New York for arranging such an outstanding regional meeting.

Forty-one pediatricians are recommended for Fellowship in the Academy.

Respectfully submitted,

OLIVER L. STRINGFIELD, Regional Chairman

PAUL W. BEAVEN, Associate Regional Chairman

### Report of Region II

Continued expansion of Academy membership in this area reflects a growing interest on the part of qualified pediatricians in the purposes and ideals of the organization. Since the January meeting at Detroit there have been sixteen completed applications submitted for consideration through regular channels. No formal regional meeting has been held since the last report. During the regular session of the Southern Medical Association at Miami, there will be a luncheon meeting for members of Region II, at which time questions pending consideration at the National Convention in Pittsburgh and problems arising from the Study of Child Health Services will be considered.

As in other sections of the country, activity during the past nine months has been primarily concerned with the organization and development of the Survey in the various states. Slow to get started in a few areas, the work has gained impetus due to the outstanding work of some state chairmen, as well as the full support of the State Medical Associations and of similar organizations. Many state pediatric societies, whose work had become disrupted during the war years, have reorganized, and their members are showing a willingness to assume responsibility for developing the program of the Academy. Florida and Virginia are outstanding in this respect. Members are actively helping in refresher courses and are serving as teachers of postgraduate medical instruction in pediatrics in addition to the duties and responsibilities of private practice. The Academy receives no outstanding identification in its activities but works through existing organizations and groups, using their facilities in attempting to promote child health.

Respectfully submitted,

WARREN W. QUILLIAN, Regional Chairman

### Report of Region III

The Child Health Services Survey is now under way in most of the states of Region III. Consequently, most of the state chairmen have little to report in regard to other Academy activities as the survey comprises a full-time job for them. The attendance of the state chairmen at the Child Health Services meeting in Chicago in September was excellent. Many perplexing problems concerning the questionnaire were ironed out during the two-day session.

Reports from Missouri, Ohio, North Dakota, and other states indicate that the Academy organization in these states is actively cooperating with various other state groups which are interested in the welfare of children.

In Illinois, Dr. Poncher has requested the Child Health Services Study committee to continue to function as an advisory committee to the Illinois State Medical Society. Such an arrangement should expediate all Academy projects in which the support and interest of all physicians in the State are desirable. Closer cooperation and planning with all agencies in the State which have to do with the health and welfare of children are anticipated. This plan might be worthy of scrutiny by all state chairmen; there is certainly a great amount of important work, much of it an accumulation of the war years, to be done in the near future. With the completion of the Child Health Services reports, the Academy organization should be ready to go smoothly ahead as a leading force in the child health activities in most of the States of Region III.

Region III now has on deposit in the First National Bank of Winnetka, Ill., funds to the amount of \$2,192.61 plus uncomputed accumulated interest since Jan. 1, 1946. Funds to the amount of \$19.07 were expended in preparatory work for the Spring, 1946, regional meeting. The regional meeting was later canceled by unanimous vote of the state chairmen.

The Treasurer of the Academy holds bonds to the credit of Region III in the amount of \$1,850.00 with a face value of \$2,500.00.

Present enrollment in Region III is 500 members. Thirty-four new applicants will be voted upon for membership at the November (1946) meeting of the Executive Board.

Respectfully submitted,  
GEORGE F. MUNNS, Regional Chairman

### Report of Region IV

Through the State Chairmen, all members of Region IV were contacted to give an opinion regarding financial support from the Academy for the International Pediatrics Congress. The results indicated that the membership was 2:1 in favor of giving some financial support by assessment of members of the Academy. However, the majority of the members felt 1947 was too early to have such a meeting; since the date has been changed to July, I am sure there will be more objections to a 1947 meeting.

A regional meeting of representatives of the various states for the Child Health Survey was held in San Francisco, September 17 and 18. This will be included in the Committee Report and Study of Child Health Care.

Respectfully submitted,  
VERNON W. SPICEARD, Regional Chairman

### Report of Region V

The principal activities after the last meeting of the Executive Board of the Academy have been devoted to informing the branches of the region about the possibilities of the celebration of the First Pan-American Pediatrics Congress and at the same time the first general meeting of Region V, both events in combination with the International Congress of Pediatrics, which will be held in New York City, July, 1947.

Since last agreement of the Executive Board of the Academy, we have sent a note to the different branches, containing all the explanation about this matter. We have decided to celebrate the meeting of Region V in Washington, D. C., three days before the Interna-

tional Congress in New York. This meeting will be presided by a head table formed by the Members of the Executive Board of the Academy and the chairmen of Region V.

The first reunion will be devoted to consideration of the internal affairs of the region, in order to establish the definite organization of Region V under the by-laws of the Academy. In this meeting, the chairman of Region V will give a general report about the region since the incorporation of the Latin-American Division to the Academy up to date.

We have sent a questionnaire to the different Latin-American countries for the preparation of a special book of the pediatric field in America, introducing to the United States the history of Latin-American Pediatrics. In this book you will find very important remarks, for example: foundation of the Latin-American Universities; the San Marcos University of Lima, the oldest in America, the University of Mexico, founded a short time later, and the University of Havana, which is also an old University with more than two centuries' existence, the special organization of the pediatric services, in their double aspect, academic, in connection with the teaching, offering a synthesis between the different pediatric schools, and in the public health aspect, referring to the organization of Children's Hospitals in America.

In the first aspect, referring to the academic field, it would be a great pleasure for me to introduce to United States pediatricians the outstanding figures, true pioneers of our pediatric sciences, Louis Morquio from Montevideo, Araoz Alfaro from Buenos Aires, Olinto de Oliveira and Fernandez Figueiras from Brazil and Angel Arturo Aballi from Havana.

In the second aspect, the social assistance, we will show you our principal units, represented by beautiful children's hospitals, as the wonderful Hospital del Nino de Mexico, the special Hospitals for Children of Chile (three new and beautiful buildings), "Pereira Rosell Hospital" of Montevideo, and the "Municipal Children's Hospital" of Havana. They are all splendid hospital units very well equipped to the specification of the Official Standard Hospital of the American Medical Association.

It would also be a very important point to consider in the pediatric field of the Latin-American countries, the goal reached by the research department, because we know very well that the general knowledge of medicine, simply applied to the diagnosis or treatment, is practically a routine if it would not be accompanied by scientific consideration, supported by research.

One of the principal points studied by the Latin-American research has been the bacteriologic aspect related with the etiology of gastrointestinal disturbances. In that aspect the Uruguayan Pediatric School is very well known. It is conducted by Professor Hormaeche, author of the very important theory called "Montevideo Doctrine" about the pathologic influence of the salmonella group against "Kiel Doctrine." The Chilean Pediatric School has also devoted very important studies about the same question and is conducted by Professors Cienfuegos and Scroggie and co-workers. In the clinical aspect of the metabolic disorders of the gastrointestinal troubles, the Argentinian Pediatric School has realized very important research which was chiefly conducted by Professor Carril and in the same question, the contribution of Professor Burghi of Montevideo and the etiological classification selected by Zervino from Montevideo too are also very outstanding. All this matter referring to the gastrointestinal disturbances in order to study the etiology, pathogenesis, and treatment has constituted the principal goal of the Cuban Pediatric School conducted by Professor Aballi and myself with the cooperation of many co-workers of our pediatric chair.

Also a point very attractive for special mention are the studies realized by Professor Agustin Castellanos in order to obtain a safe vital diagnosis of congenital heart diseases by means of the "opaque angiocardigram." This method permits the visualization of the heart after the introduction of the opaque substance in the vein of the arm in a first view which we call angiodextrocardiogram because it only shows the right heart. A few seconds later we can obtain a second view which shows the left heart with the gross vessels which we call angiolevocardiogram. This method permits at the present time to establish a positive and real diagnosis of all cardiac malformations.

Complete information of etiology and production of the important phenomenon of the atelectasis and its influence on many different lung troubles is also a brilliant point of the



Latin-American Pediatric Research. In that sense, the studies of Professor Valledor of Havana, Professor Vacarezza of Buenos Aires, and Professor Scroggie of Chile represent a very nice contribution.

After considering the great development of scientific centers of the Latin-American countries, we will include a relation of the different international connections represented by many filial associations of important United States Associations; The American Academy of Pediatrics, The A. M. A., The A. P. H. A., The P. A. M. S., and finally the great importance of political connections represented by the Pan-American Union and, particularly in the medical field, by the Pan-American Sanitary Bureau, which has been, perhaps, the most important link in the last ten years among the scientific research centers of America.

For all these reasons we consider that our program to realize the first Pan-American Pediatric Congress will be a firm step over the way of a cordial and positive friendship among all our countries, supported and conducted by the purest link among human dignity; that is, science and country friendship.

We hope that this effort of the Latin-American Group will be received with deep sympathy by our fellows of the United States to whom we devoted our best wishes and efforts.

After these Pan-American Pediatric Meetings, we will continue together in the work for permanent improvement of Region V as members of the great family of the American Academy of Pediatrics.

Respectfully submitted,  
FÉLIX HURTADO, Regional Chairman

### Report of the Secretary

During the past year, the Academy has launched forth upon an effort which is probably as ambitious as any that has ever been attempted by a small group in the United States. Of course, I am speaking of the survey of child health services. If we are to have local or national legislation, this legislation should be based on facts and not suppositions, and it is with that in mind that the Academy has undertaken this survey. The cooperation of all the members and the exhaustive work carried out by the state chairmen is something of which the Academy may well be proud. I think that all of us will say the right man was chosen when Dr. John P. Hubbard was put in charge, and we must credit him with much of the success, but no man alone without the cooperation of cohesive organization could have brought about the results which have been attained in this instance. The organization of the Academy on a state basis has justified itself.

The International Congress of Pediatrics, as at present projected, will occur in July in New York City. This has materially altered the plans of the Academy to hold a Pan-American Congress in 1948. However, thanks to the activities of the men in Washington, especially Dr. Edgar P. Copeland and Dr. Joseph S. Wall, we are well on the way to arranging a preliminary meeting of the Latin-American groups under the Chairmanship of Dr. Félix Hurtado. This will occur in Washington just previous to the International Congress. The final arrangements for the meeting have not yet been made.

Due, more than most of you realize, to the efforts of Dr. Joseph S. Wall, the legislation for National Governmental Control of Child Health Agencies and, in fact, of the whole picture of medical attention to the child has been at least temporarily avoided. Most of us felt that this was striking at the very heart of child health in this country and that it would have been a disastrous move for the children, and we may congratulate ourselves that one of our own group was so prominent in preventing this legislation.

You will be asked at this meeting to vote on the question of redistricting of the Academy. This, to my way of thinking, is long overdue. The present arrangement does not give equal representation on the Executive Board and while there is slight discrepancy in the new arrangement, it is far better than the old. The Secretary hopes that this arrangement can be brought about. If it is, the Secretary's office will take over subsidiary meetings in different parts of the country, in addition to the National meeting which is already carried on in his office.

Dr. James G. Hughes has taken over the Chairmanship of the liaison Committee with the American Legion. With the members of the Academy who have come out of service this will be of especial interest. The Legion has funds to carry on child care work throughout the country, and it wishes direction of the American Academy of Pediatrics in carrying this out. Unquestionably, when our survey is finished and properly recorded, such an affiliation will result in great benefit to the children of the country and it is to be hoped that we can have active affiliates in each state to promote and direct the action of the Legion.

For several years now, the Academy has been mulling over the question of a library and museum. The material for the library is available and there are accumulating many museum pieces, as well. While the library will not be able to finance this from its own funds, it seems likely that our friends in many activities will be willing to provide a sufficient fund so that a building can be erected. It will be necessary, however, to provide funds for carrying this on and at the present time the method of doing this has not been determined.

A change has come with respect to the services which we have been rendering to Region V members. We have done away with the abstracts in Spanish and the dues have been raised to \$10.00 for all members. This will enable us to pay the expenses of a representative from that Region to at least one of our Executive Board meetings each year, preferably that held at the time of the annual meeting. It is to be hoped that this solution will meet the approval of Region V, which it seems to have, and will also make for closer relationships in the Academy.

The men in service are coming home and from a high of nearly 400 members there are less than seventy now in service. It is gratifying to know that nearly all of the men who have come back have stepped into practice and are doing well. The chief difficulty has been to find a place to live, but that, I think, has been satisfactorily solved by most of them.

It is now my unpleasant duty to report to you the names of those who have left us since the last meeting: Arthur W. Benson, Troy, N. Y., Murray B. Gordon, Brooklyn, N. Y., Harold C. Joesting, Los Angeles, Calif., Harold O. Ruh, Cleveland, Ohio, Dr. Stewart H. Welch, Birmingham, Ala. Emeritus Fellows: Stanley D. Giffen, Toledo, Ohio, Homer Woolery, Bloomington, Ind., and Harry R. Lohnes, Buffalo, N. Y.

Respectfully submitted,  
CLIFFORD G. GRULEE, Secretary

### Report of the Treasurer

*(For this report, see following page.)*

It was voted by the Executive Board that after the February meeting the traveling expenses and \$10.00 per diem for each appearance on the program be given for each participant in the general program and for one participant in each round table.

It was voted that hereafter committee reports be distributed only at the Annual Meeting and not be sent out previously to the members, since they are published in the JOURNAL.

The request of Herbert C. Miller of Kansas City for recognition by the Executive Board of his attempt to gain information concerning the incidence of congenital anomalies associated with rubella infections in the mother, and in the second place to obtain information which will help in setting up more intensive studies in case our survey indicates that the problem is a fairly extensive one was approved by the Board with the request that questionnaires not be sent out until after our survey is completed.

The Executive Board approved the appointment of a representative to the National Commission on Child Health set up by the President.

Dr. Hugh McCulloch was present in person to discuss the question of publication of the JOURNAL. This was discussed quite extensively and it was decided to wait for the recommendation of the Editorial Board at the meeting of the Academy in February.

Mr. Lawrence J. Linck, Executive Director of the National Society for Crippled Children and Adults, Inc., requested in person the appointment of a liaison officer to that group by the Academy. His request was granted and George F. Munns was appointed by the president.

# Report of the Treasurer

## STATEMENT OF RECEIPTS AND DISBURSEMENTS, JULY 1, 1946, TO OCT. 30, 1946

Balance in checking account, July 1, 1946	\$11,187.49
Balance in savings account, State Bank & Trust Company	8,214.89
Balance in savings account, First National Bank & Trust Co.	1,560.09
	<u>20,962.47</u>

### Receipts:

Dues	\$39,658.13	
Wartime Assessment	15.00	
Exhibits—November, 1946 Meeting	4,640.00	
Annual meeting registration, November, 1946	4,180.36	
Annual meeting round tables, November, 1946	1,494.38	
Initiation fees	1,925.00	
Interest earned	327.50	
Pamphlets—Child Health Record	\$ 204.25	
Immunization Procedures	116.08	
Vitamins	6.00	326.33
Subscriptions—men in service		<u>100.00</u>
		52,666.70
		<u>\$73,629.17</u>

### Disbursements:

Annual Meeting—November, 1946	\$ 800.96	
Bank charge and exchange	44.84	
Certificates and mounting	48.56	
Executive board	647.16	
Miscellaneous	109.30	
Office supplies and equipment	106.24	
Postage	163.54	
Rent	778.50	
Salaries—Secretary	\$4,000.00	
Assistant Secretary	666.66	
Stenographer	1,000.00	
Office	785.00	6,451.66
Stationery and printing		231.04
Subscriptions		9,629.81
Telephone and telegrams		277.54
Travel—Secretary		12.77
Treasurers' bonds		62.50
Expense—regions	\$ 158.96	
States	77.03	
committees	975.53	1,211.52
Pamphlets—Child Health Record	21.55	
Immunization Procedures	3.55	24.90
		<u>20,600.84</u>
		<u>\$53,028.33</u>

Balance in checking account, October 30, 1946	\$41,328.35
Balance in savings account, State Bank & Trust Company	10,139.89
Balance in savings account, First National Bank & Trust Co.	1,560.09
	<u>\$53,028.33</u>

## Reports of Committees

Warren R. Sisson and John P. Hubbard reported on the Study of Child Health Services. A committee was appointed to choose a publicity expert for the use of the Committee for the Study of Child Health Services.

Report of the Committee for the Study of Child Health Services<sup>2</sup>

## BUDGET FOR GRANT OF \$116,000 FROM NATIONAL FOUNDATION FOR INFANTILE PARALYSIS

	BUDGET FIRST YEAR	EXPENDED TO 10/31/46	BALANCE REMAINING	BUDGET SECOND YEAR
Salaries:				
Regional directors	\$19,000.00	\$13,946.38	\$ 5,053.62	\$16,000.00
Travel:				
Regional directors	6,000.00	3,567.52	2,432.48	3,000.00
Salary:				
Administrative Asst.	3,000.00	2,142.54	857.46	3,000.00
Salaries:				
Stenographers	4,000.00	2,422.73	1,577.27	4,000.00
Office				2,000.00
Supplies				
Printing	8,000.00	8,000.00		5,000.00
Telephone & telegraph				
Postage				
Educational survey	15,500.00	806.93	14,693.07	15,500.00
Statistical dept.	12,000.00	11,856.24	113.76	
Totals	\$67,500.00	\$42,772.34	\$24,727.66	\$48,500.00

## ESTIMATED BUDGET FOR STATISTICAL ANALYSES (National Institute of Health Account Oct. 1, 1946, to Dec. 31, 1947)

ITEM	NUMBER OF PERSONNEL	ANNUAL RATE	OCT. 1, 1946, TO JUNE 30, 1947 (9 MONTHS)	JULY 1, 1947 TO DEC. 31, 1947 (6 MONTHS)	TOTAL
Professional personnel:					
Chief of research section	1	\$5,000	\$ 6,000	\$ 4,000	\$ 10,000
Operations supervisor	1	5,000	3,750	2,500	6,250
Assistants, statistical	3	3,600	8,100	5,400	13,500
Total			\$ 17,850	\$ 11,900	\$ 29,750
Clerical personnel:					
Machine supervisor	1	3,600	2,700	1,800	4,500
Coders <sup>2</sup>	39	2,400	70,200	-	139,800
Coders <sup>2</sup>	58	2,400	-	69,600	
Keypunch operators	2	2,400	3,600	2,400	6,000
Computers	8	2,400	14,400	9,600	24,000
Clerk typists	2	2,400	3,600	-	13,200
Clerk typists	8	2,400	-	9,600	
Total			94,500	93,000	187,500
Total personnel			112,350	104,900	217,250
Rental and equipment:					
Office rent, 4,000 sq. ft.		\$2/sq. ft.	9,000	-	18,000
Office rent, 6,000 sq. ft.		3/sq. ft.	-	9,000	
Machine rental		3,400	2,700	3,100 <sup>3</sup>	7,800
Office equip. and supplies			4,500	2,200	6,700
Total			16,200	16,200	32,500
GRAND TOTAL			\$128,550	\$121,200	\$249,750

<sup>1</sup>Rental for keypunches, collators, sorters, tabulators for six months prior to July 1, 1947, and six months thereafter.

<sup>2</sup>See justification for number of coders on next page.

<sup>3</sup>Represents one additional sorter and one additional tabulator for this period.

## AUDITOR'S STATEMENT

November 15, 1946

To the Executive Board  
American Academy of Pediatrics  
Evanston, Illinois  
Gentlemen:

I have examined the budgets presented by the American Academy of Pediatrics, Study of Child Health Services as of October 31, 1946, for the National Foundation for Infantile Paralysis account, the National Institute of Health account, and the General Academy account.

The amounts represented as having been spent have actually been paid out. The budget estimates seem fair and reasonable and are not excessive viewed in light of past experience and future requirements.

In my opinion the accompanying budgets present fairly the requirements necessary for the fulfillment of the program outlined for the Study of Child Health Services.

Verly truly yours,  
MAX R. BYERS  
Certified Public Accountant

Washington, D. C.

## AMERICAN ACADEMY OF PEDIATRICS STATISTICAL ANALYSES

*Budget Estimate for Coders, Oct. 1, 1946, to Dec. 31, 1947*

It is estimated that 700 man-months of clerical time will be required for editing, math checking, coding, transcribing, and verifying these processes. To complete half of this work before July 1, 1947 (nine months), and the balance by Dec. 31, 1947 (six months), would require:

39 coders @ 9 months each or 351 man-months, and  
58 coders @ 6 months each or 348 man-months

Total 699 man-months

The basis for these estimates is shown below:

SCHEDULE	ESTIMATED NUMBER OF SCHEDULES	NUMBER OF PUNCH CARDS PER SCHEDULE	TIME PER PUNCH CARD
I-A	10,000	3	30
I-D	5,000	4	30
I-E	600	2	30
I-F	500	2	30
I-G	200	2	30
I-H	100	2	30
I-J	100	2	30
II-A	7,000	2	20
II-B	3,500	2	20
II-C	3,500	1	20
II-D	7,000	2	20
II-E	3,500	1	20
II-F	7,000	2	20
II-G	7,000	2	20
III-A	181,000	1	15
III-B	4,000	3	30
III-C	70,000	1	15

## BUDGET FOR GENERAL ACADEMY ACCOUNT

Contributions Received for First Year:	
American Academy of Pediatrics Reserve Fund	\$18,000.00
Mead Johnson & Company	18,000.00
M & R Dietetic Laboratories, Inc.	10,000.00
Carnation Company	10,000.00
Pet Milk Company	10,000.00
New England Pediatric Society	500.00
Lederle Laboratories	5,000.00
Field Foundation	5,000.00
Cutter Laboratories	500.00
Total Receipts	\$77,000.00
Less: Amount expended for Study prior to February, 1946	4,474.16
	\$72,525.84

## BUDGET FOR GENERAL ACADEMY ACCOUNT (CONT'D)

	BUDGET FIRST YEAR	EXPENDED TO 10/31/46	BALANCE REMAINING	BUDGET SECOND YEAR
Salaries	\$18,000.00	\$13,238.44	\$ 4,761.56	\$22,000.00
Travel:				
Executive staff and committee	5,000.00	4,506.31	493.69	5,000.00
Furniture and fixtures	4,000.00	771.77	3,228.23	2,000.00
Postage	1,000.00	189.23	810.77	1,000.00
Office supplies	2,000.00	336.70	1,663.30	1,000.00
Office maintenance	600.00		600.00	2,400.00
Printing	3,000.00	1,501.65	1,498.35	3,000.00
Publicity	1,000.00	326.39	673.61	1,000.00
Committee report:				
Publishing and distribution				5,000.00
Telephone and telegraph	1,000.00	177.62	822.38	1,000.00
Periodicals and books	100.00	23.65	66.35	100.00
Car purchase and travel	2,000.00	2,643.81	643.81	1,000.00
Social Security	400.00	53.84	346.16	400.00
Accounting and legal:				
Accounting and auditing	600.00		600.00	1,800.00
Premium on bonds	400.00	187.50	212.50	400.00
Legal fees	200.00		200.00	200.00
Insurance	100.00		100.00	300.00
Miscellaneous	250.00	184.82	65.18	250.00
State programs	30,000.00	16,870.02	13,129.98	30,000.00
Educational study:				
Field staff	1,000.00		1,000.00	5,000.00
Travel and committee meetings	1,500.00		1,500.00	3,500.00
Totals	\$72,150.00	\$41,021.75	\$31,128.25	\$86,350.00

## COMMENTS

*General Academy Account.—*

1. The Field Foundation has made a grant of \$10,000 for a two-year period, of which \$5,000 has been received. At the time the first payment was received, the following conditions were made by the Field Foundation:

- (a) "That the first \$5,000 of this Corporation's contribution be applied to the nation-wide Study of Child Health Facilities and Services by states.
- (b) "That the second \$5,000 of this Corporation's contribution be applied toward the compensation of competent personnel to publicize the results of the survey in the daily press, in magazines, on the radio, and through other channels of public information."

In accordance with these conditions, the first \$5,000 already received has been applied against the operating cost of the development and conduct of state programs for the Study of Child Health Services. The second \$5,000, to be received during the second year, will be applied in accordance with paragraph (b) above.

2. Expenditures budgeted for the National Foundation Account were met from the General Academy Account prior to the receipt of the grant from the National Foundation.

3. Item 1 (Salaries) on the general Academy budget includes:

The salary of the Director, starting Jan. 1, 1946,

All other salaries prior to the receipt of the grant from the National Foundation for Infantile Paralysis,

Entire statistical pay roll for the month of October, pending the receipt of the NIH grant,

Other personnel of the Administrative Staff not included in the Foundation budget, Compensation of publicity personnel during the second year in accordance with the conditions of the Field Foundation.

4. Item 8 (Publicity) includes the printing and distribution of progress bulletins, exhibits, etc.

5. Item 16 (State Programs) includes payments advanced to state chairmen in those States where local resources have been inadequate to meet full expenses of state study programs. When the original estimates for state budgets were made, state reports were not anticipated, and hence no provision was included for the cost of their preparation and publication. After reviewing the financial reports of those States which have completed their programs, it is evident that either their finances are completely exhausted or that the remaining balances are too small to meet the cost of their state reports. For this reason the budget of the Central Office for the second year shows an amount of \$30,000 to insure that sufficient funds will be in hand to enable all States to prepare satisfactory reports. This item for state programs has resulted in a budgetary deficit of \$41,350 which is needed to meet budget requirements over and above the \$45,000 pledged for payment in this account during the second year.

#### *Foundation Account.—*

1. In order to meet expenditures of the statistical division prior to the receipt of the grant from the National Institute of Health, the National Foundation was requested to allow \$10,000 to be taken from Item 6 (Regional Directors) and \$2,000 from Item 9 (Office). This request was approved by letter dated June 4, 1946.

2. In order to meet current printing expenses, the National Foundation was requested to allow \$3,000 to be taken from Item 6 to be applied against Item 11. This request was approved by letter dated Aug. 19, 1946.

#### *National Institute of Health Account.—*

The first payment from the National Institute of Health grant was made on November 1 in the amount of \$128,550. Since this amount was budgeted for the period Oct. 1, 1946, to June 30, 1947, permission has been received to make payments from this account in arrears, starting with Oct. 1, 1946. Expenditures to be included from this budget have been met from the General Academy Account and will be refunded to the General Academy Account following the establishment of the NIH Account at the Bankers Trust Company of New York.

#### RECOMMENDATIONS TO EXECUTIVE BOARD

The Committee for the Study of Child Health Services, at a meeting in Washington, Oct. 1, 1946, unanimously agreed that the following recommendations should be made to the Executive Board of the Academy:

- (a) That all factual material arising from the Study of Child Health Services should be released by the American Academy of Pediatrics at both National and State levels.
- (b) That the Committee for the Study of Child Health Services is responsible not only for preparing a national report of the factual material but also for submitting to state chairmen tabulated factual data suitable for the preparation of state reports.
- (c) The state chairmen together with their advisory committees are responsible for seeing that state reports based upon the tabulated material are written and published as soon as possible. Whereas the national report prepared by the Committee for the Study of Child Health Services will include no recommendations arising from the data, the state reports may and should include recommendations based upon local situations.
- (d) That within a period of two months after receipt of the tabulated material, state chairmen should be required to submit to the Committee for the Study of Child Health Services a statement indicating that definite plans have been made to write a state report and a brief description of such plans. If at the end of this two months' period the state chairman has not made satisfactory plans to report the material arising from the Study in his State, the Committee for the Study of Child Health Services is free to release the factual data to any person or group qualified to use it within the State. If the plans for the preparation of the state report are considered by the committee to be satisfactory, then the state chairman should be

- allowed an additional period not to exceed four months to complete the state report during which time none of the factual data pertaining to his State should be released to others by the Committee for the Study of Child Health Services except after obtaining approval from the state chairman concerned.
- (e) That after a period of six months following the receipt by the state chairmen of the tabulated material, the Committee for the Study of Child Health Services is free to release the tabulated material or punch cards to any person or group qualified to use it.
  - (f) That a further committee of the Academy should be created which would be responsible for the recommendations arising out of the Study at the National level and for developing from the Study a suitable action program. This committee would also be responsible for reviewing the recommendations contained in state reports, advising in the use of the material in the respective States, but would have no veto power over any recommendations in state reports.
  - (g) That because of the great importance of the proper implementation of the factual data secured, both at the National and the State level, it is considered necessary that the Academy employ a full-time executive director to direct the use of this material in the States and also at the National level. This executive director should be the executive secretary of the new committee referred to in the paragraph above.
  - (h) That in the case of North Carolina, the Pilot State, the Committee for the Study of Child Health Services should be responsible not only for the factual report but also for reviewing the recommendations contained therein.
  - (i) That in publication of State as well as National reports, credit should be given to the United States Public Health Service and the Children's Bureau for the cooperation they have given to the Academy in the Study. Acknowledgment should also be made of contributions or cooperation in the form of services and financial support from other sources.
  - (j) That after publication of National or State reports the factual material should be available to anyone desiring to use it.

The Report of the Committee on the Study of Child Health Services was approved except for section "g" which was to be acted upon at the meeting of the Executive Board in February at Pittsburgh.

### Report of the Committee on School Health

#### FURTHER COMMENTS UPON STANDARDS FOR SCHOOL MEDICAL EXAMINATIONS

Repeated inquiries regarding standards for medical examinations and school health service have come to the Committee on School Health. These inquiries are difficult to answer satisfactorily because the quality of medical examinations in schools depends so much more upon the number of children to be examined, the time given by the physician, and the conditions under which the physician works, than any set of standards for the examination. Furthermore, there is a tendency to overemphasize the examination and neglect what comes after it.

While the brochure prepared by the Committee on Cooperation with Non-Medical Groups and Societies of the Academy\* indicates in a brief and concise manner the minimum standards which the Committee feels should be included in a reasonably thorough health appraisal of a school-aged child, a different approach is needed for the adolescent boy or girl.

However, it must be recognized that under the pressure of waiting parents, the demands of school authorities, or administrative convenience, many short cuts are tolerated so the child may fail to benefit from the physician's full knowledge of the history or enough advice to the parent about behavior problems. Laboratory procedures are usually omitted in school and the chest x-ray which is particularly indicated in high schools, because of the educational opportunities offered by the activity, is only beginning to be accepted as a regular procedure.

\*Printed and distributed by Mead Johnson and Company in cooperation with the American Academy of Pediatrics.



In a school situation time is saved by identification data and the vision and hearing test records being prepared by the nurse or teacher, but the time required for a careful history and such explanation to the parent as to insure understanding and cooperation cannot be avoided without serious loss of benefits to many children.

We have, in previous reports, pointed out how the attempt to give annual or too many routine examinations may interfere with the quality of medical judgment, and the time given by the physician in the school is dependent upon the remuneration and the plan of the service. The presence of the parent at the examination takes more time and yet is essential for the history and for interpreting the needs of the child so that the parent is persuaded to obtain service. Many, if not most, parents who can afford private care prefer to obtain the health examination in the private office of their family physician or pediatrician, particularly when the medical profession is alert to the possibilities of health supervision.

No fixed rule can be applied as to the frequency of medical examinations in school and still maintain an appropriately high quality of medical judgment. Too often the physician does not have enough time to give as much as fifteen or twenty minutes per pupil and parent, and yet double that time may be required to get all the background of a case with special problems and to help the parent, teacher, and nurse understand the problem. Naturally, the larger the proportion of children from the higher economic status homes will respond with more private office examinations and schools with many poor children will require more examinations and more follow-up in school. The decision as to the frequency of the examinations should be a medical decision based upon the budget allowed for medical time, the assistance given to the physician, nursing time for follow-up as well as the socioeconomic status of the children.

Certainly, all children should have an examination on entrance to school and thereafter as often as the teacher and nurse observe signs and symptoms or behavior suggesting a medical problem. More routine examinations should not be attempted unless there is a real prospect that the physician will have time enough without interfering with the quality of this much service. Of course, if staff time enough is available, more routine examinations would be desirable, but we would emphasize the need for study of the cases referred by teachers and nurses and for parent attendance at the examination, because the tendency has so generally been to achieve quantity rather than quality. Furthermore, the referred cases are more likely to be in need of medical attention and a large proportion would not be discovered by routine examinations. Proper encouragement of teachers to observe the conditions needing the medical judgment of the school physician should probably lead to twice as many children referred to the physician as are required for routine examinations on entrance to school. While no adequate evidence is available as to the expected number of children that should be referred by teachers and nurses, there is plenty of evidence\* that there is need for such examinations apart from the provision for routine examinations. In giving emphasis to time for study of referred cases, there should be no assumption that complete coverage of all the children at entrance to school should be the only objective for routine examinations. The next step, no doubt, should be to cover all children before leaving school, and the administration of such a service should be responsible for encouraging a larger measure of protection and health service for all children.

As inadequate remuneration and inadequate time so often interfere with the quality of medical judgment and the usefulness of the service, it is well to review briefly some essentials of the physician's service in the school not usually included in estimates of medical time:

1. Time must be provided for the physician to consult with the nurse, principal, and teachers on problems that arise concerning communicable disease as well as to inspect children referred because of suspicion of contagion during the period he is in the school.

\*George M. Wheatley, M.D.: Case finding Procedures Developed by the Astoria School Health Study "The Child," U. S. Children's Bureau, vol. 4, nos. 11 and 12, May and June, 1940.

Dorothy B. Nyswander, Ph.D.: Solving School Health Problems, New York, The Commonwealth Fund.

National Committee on School Health Policies of the National Conference for Cooperation in Health Education: "Suggested School Health Policies," ed. 2., revised, Health Education Council, 10 Downing Street, New York 14, N. Y., pp. 26-28, 1946.

2. Time for diphtheria or immunization and vaccination service, naturally, will vary in different schools and according to community policy.

3. The time necessary to consult with the principal and teachers is dependent upon the resourcefulness of the physician and his understanding of school problems, but there is no doubt about the need of medical advice both on individual children and on curriculum, health teaching, hazards, seating and lighting, ventilation, mental and emotional health, school food service, and many other questions that arise in school.\*

4. The medical reports from private and clinic physicians should be reviewed by the school physician and interpreted to the nurse and other members of the school staff, who are concerned.

5. Correspondence or telephone calls with practicing physicians are an essential part of the service of the school physician to correct misunderstandings and to exchange essential information concerning individual children that are known to both the school physician and the practitioner.

6. In any program that provides for the parent to consult with the physician at the time of a school examination, and for the medical appraisal of children referred by the teacher and nurse, there must be planning for the schedule of cases to be seen by the school physician. This requires time for a review of the day's records and advice to the nurse concerning the proper allotment of time for the various activities of the physician's session.

7. Finally, the physician should have time allotted to discuss with the nurse the problems met in the course of her follow-up, to influence the parent to meet the needs of the child. This advice is concerned not only with decisions for release from follow-up but to give the nurse additional information necessary for the education of the parent or a better understanding of the problem, as well as decisions for further observation, re-examination, or further investigation as to home or other environmental conditions.

These seven items have been estimated as requiring at least one-fourth of the physician's time in a well-directed service.†

Other conditions under which the physician works that influence the time requirement include facilities for privacy and disrobing of pupils, the available records of causes of sickness absences, records of vision and hearing tests, height and weight records, teacher observation records, dental service records, and monitor service to send for pupils, waiting room for parents and the assistance of the nurse to report on her knowledge of the case and to insure that all records are available and that she understand the advice to meet the needs.

While it should be obvious that the physician must have time enough to avoid hasty judgments, and pay enough to attract the best ability, good physicians do not want to spend their time on routine work that does not yield experience which contributes to their professional development. The presence of the parent in school offers some interest and challenge to the physician in persuading and educating parents in the health care of their children. He should learn to make parents appreciate the value of advice and supervision of well children. With well-selected referral of children likely to be in need of medical care, he should meet a good number of challenging problems as to the degree of seriousness of adverse conditions discovered by him.

To carry out such a program, the physician must meet a definite weekly schedule of hours throughout the year so that the terms of his employment and remuneration should be computed on the basis of hours needed per week for each school according to the number and economic status of the pupils. To improve this remuneration should benefit the whole profession through improved public relations and public education. The pay for Veterans Administration service should immediately influence the pay for school physicians. To meet the variations in different parts of the country it is suggested that the physician should be paid at a rate for each hour of service at least equal to the average for an office visit to a qualified pediatrician in the community.

\*Op. cit. pp. 11 to 38. "Educational Qualifications of School Physicians," American Journal of Public Health, vol. 34, no. 9, 1944.

†Unpublished paper presented at Joint Session of the School Health and Vital Statistics Sections of the American Public Health Association Meeting in New York, October 4, 1944.

In order to offset the routine character of part of the work, to improve the service, and to extend postgraduate medical education, the time schedule should also provide for such in-service training by competent clinical instructors as will improve the knowledge of the physician in those special fields of medicine concerned with problems common to school age children. Groups of children selected by the school physician should provide excellent teaching material for clinical instruction by the pediatrician, the cardiologist, the orthopedist, the otologist, the ophthalmologist or the child psychiatrist. The dentist and dermatologist may also participate to advantage. The best way to advise parents, nurse and teachers as to the needs of children is a subject for round-table discussion that can not only benefit the school program but the quality of health education by the physicians in their private practice. The scope of problems presented by children in school offers a field for clinical teaching of preventive pediatrics not generally used, but the screening by teachers and nurses and, in turn, by the school physician should reveal such a selection of cases as to indicate new opportunities and a new interest in the whole child. Consultation services of specialists would not only increase the interest of the physician but insure sound advice for guidance of the parent in the use of the community medical services.

Just as pediatricians demonstrated new possibilities for service to children in the schools of a generation ago, so today they may demonstrate a broader field of service by postgraduate medical education for young physicians who work in the schools. With part-time employment and limited tenure of school physicians this contribution to improved health service should eventually be available to all physicians who serve children.

Respectfully submitted,  
 HAROLD H. MITCHELL, Chairman  
 ROCKWELL M. KEMPTON  
 A. CLEMENT SILVERMAN  
 ARTHUR E. WADE  
 ESTELLE F. WARNER  
 GEORGE M. WHEATLEY

The report of the Committee on School Health by Harold H. Mitchell was accepted and Dr. Mitchell was congratulated upon the excellence of his report. His suggestion that we cooperate with the National Conference for Cooperation in Health Education through a liaison officer was accepted and he was appointed liaison officer to that group.

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*After consultation with Mr. William F. Kirk of the Hotel William Penn, and Mr. Adolph O. Frey of the Pittsburgh Chamber of Commerce, it was decided to hold the Annual Meeting Feb. 24 to 27, 1947, at the Hotel William Penn.*

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#### Report of the Committee on Contact Infections

The committee does not feel it feasible to undertake large scale investigation of ultra-violet air sterilization in institutions.

Respectfully submitted,  
 REGINALD A. HIGGONS, Chairman  
 GAYLORD W. GRAVES  
 PARK J. WHITE

The report was accepted.

#### Report of the Committee on Fetus and Newborn

The present committee, having recently been appointed, has been unable as yet to meet and undertake a program.

The committee plans to meet in Pittsburgh and is anxious to undertake a vigorous program directed toward a general reduction in fetal and neonatal mortality.

The committee wishes to remind the members of the Academy that it is anxious to receive questions or suggestions from the members.

Respectfully submitted,  
STEWART H. CLIFFORD, Chairman  
NINA A. ANDERSON  
ETHEL C. DUNHAM  
JOHN C. MONTGOMERY  
HOWARD J. MORRISON  
MILTON J. E. SENN  
CHARLES A. WEYMULLER

The report was accepted.

### Report of the Committee on Governmental and Medical Agencies

The committee has held no meeting since the June report, but will hold a meeting on Thursday, Nov. 14, 1946, at Pittsburgh on the following agenda, which it is proposed that the committee carry out during the coming year.

1. Reactivation of forty-eight state committees and their state programs.
2. Report on Advisory Aid to Bureau of Food and Drugs, Federal Security Administration (Dr. Harrold Murray).
3. Implementation of Academy-approved national program.
4. A winter conference in New York or Washington of our Committee, with its conference members from the American Medical Association, United States Public Health Service, Children's Bureau, and invited guests, to discuss "National planning and standards for good pediatric medical care for all children in the United States, with particular consideration of children in families unable to pay for medical services, to the end that the standards of medical care may be maintained at a high level among such groups."

*Note:* Members of the committee are urged to give serious study to this key problem of how "standards of pediatric medical care may be maintained at a high level among those groups unable to pay for medical services," in accordance with the resolution herein quoted, adopted by the Academy in Detroit in January, 1946.

It is our desire that the committee initiate a conference study, by governmental and medical agencies, of specific factors influencing standards of quality of pediatric medical care, and thus make a constructive contribution to the Academy's Child Health objective of better child health, by focusing attention on the kind of pediatric care which now obtains in the various forms of child health services now available. The cooperative conference study by governmental and medical agencies might well serve to clarify our thinking and planning and aid in bringing all concerned with child health to constructive action on whatever "areas of agreement" as may be reached, because all of us wish good quality pediatric medical care in all types of child health services.

The splendid cooperation of governmental and medical agencies, national and state, now being shown in the monumental study of Child Health Services, is laying a sound foundation for continued teamwork when the study is finished. It will be the desire of our committee, strengthened in 1946 by the addition of two of the best pediatric brains in the country, to supplement the Academy's fact-finding study by our conference committee's studies of what should be the standards of pediatric medical care which would maintain high quality in all present kinds of child health services.

Respectfully submitted,  
STANLEY H. NICHOLS, Chairman  
PAUL W. BEAVEN  
W. L. CRAWFORD  
WILBERT C. DAVISON  
ALEXANDER T. MARTIN  
HARROLD A. MURRAY  
OSCAR REISS  
A. L. VAN HORN  
JOSEPH S. WALL

The report of the Committee on Governmental and Medical Agencies was accepted, and Stanley Nichols was asked to defer action until such time as the matters in dispute could be referred to the proper committee of the Academy which was to be appointed.

### Report of the Committee on Legislation

The membership of the Academy is familiar with the fact that the year 1946 has been characterized by a plethora of legislative proposals concerning medical care.

Of the several bills introduced and under committee consideration by Congress, one was enacted and signed by the President, S.191, the Hill-Burton Bill. The initial phases of State surveys as to hospital and health center needs will shortly be undertaken under the jurisdiction of the United States Public Health Service.

S.2143, the Taft-Smith-Ball Bill, did not reach the stage of hearings during this session of the Congress. Its conservative provisions have met with considerable support from members of the medical profession who approve of its principles and urge its further study.

On May 31, 1946, the Chairman of the Committee on Legislation was finally permitted to testify before the Senate Committee on Education and Labor holding hearing on S.1606 (the Wagner-Murray-Dingell Bill) and to present a statement for the record.

The report of the Legislative Committee to the Executive Board upon the occasion of its June 7 meeting has been published in the September number of the JOURNAL OF PEDIATRICS, pages 387 to 397 and needs no repetition here, as this report summarizes committee activities up to that date.

No doubt sensing the failure to secure passage of S.1606 before the adjournment of Congress, a desperate last-minute attempt by the proponents of this type of legislation was made in early June by shifting hearings to the House side of Congress in order to obtain, if possible, favorable action on S.1318, introduced by Senator Pepper and associates, but for political reasons also introduced in the lower house by four or five cosponsors.

On June 7, the chairman of the Committee on Legislation testified before the House of Representatives Committee on Labor, Subcommittee on Aid to the Physically Handicapped under the chairmanship of Congressman Augustine B. Kelly, the chairman being the only member of the House committee present, although a favorable report was ultimately made recommending the passage of H.R.3922 (identical with S.1318) after most perfunctory hearings lasting but a few hours, which gave no opportunity to hear from but a handful of witnesses.

On June 18, Senator Pepper suddenly promulgated hearings by the Senate Committee on Education and Labor on his own bill, S.1318, having sent out a flood of telegrams urging the friends and supporters of this legislation to march on to Washington like a veritable "bonus army," analogy not without some basis of truth!

Your chairman appeared before this hearing on behalf of the Academy and the American Medical Association at the latter's request. The testimony presented by witness together with supporting written statements forms a book of some 391 pages titled *Maternal and Child Welfare; Hearings before the Committee on Education and Labor, United States Senate, Seventy-ninth Congress, Second Session, on S.1318*. A copy may be obtained by writing to the Chairman, Honorable James E. Murray, or from your respective State Senators.

Efforts to secure enactment of S.1606 and S.1318 were abandoned in early July. Senator Pepper's Subcommittee on Health and Education was also dissolved by Congress on June 29.

As reported in the *New York Times* of July 16, 1946, to quote: "The Senate Education and Labor Committee sidetracked plans for substantial changes in child welfare laws July 15 and voted instead to attempt merely to increase funds for these services. The committee delegated Senators Pepper and Taft to confer with Senator Walter F. George, Chairman of the Finance Committee, on a resolution for the money."

In accordance with this directive, Senators Pepper and Taft introduced Joint Resolution No. 177 to effect increase in funds allotted to maternal and child health and welfare services under the present Title V of the Social Security Act. The amended Social Security Act, passed by the Congress on August 2 and signed by the President on August 10, almost

doubles the existing funds carried under Title V, a break-down showing an increase of the total annual authorization for maternal and child health services from \$5,820,000 to \$11,000,000 and for crippled children from \$3,870,000 to \$7,500,00. The total amounts annually authorized for each program are equally divided between funds A and B, and as a result the proportion of the total which must be matched is considerably less than the proportion under the previous authorizations. For the fiscal year 1947, the Congress appropriated \$1,660,000 MCH Fund A; \$3,520,000 MCH Fund B; \$880,000 Crippled Children's Fund A; and \$2,750,000 Crippled Children's Fund B, in addition to the amounts previously appropriated for the current fiscal year.

In lieu, therefore, of the radical changes proposed under legislation introduced in the 79 Congress, that body enacted legislation along the lines advanced and advocated by the Academy in its resolutions adopted at the Detroit meeting in January, 1946, namely: "Pending the completion of this study (Study of Child Health Services), it is recognized that urgent needs exist in some States that should be met in the immediate future. To this end the Academy recommends that additional Federal funds be made available for grants-in-aid to the States under existing Maternal and Child Health and Crippled Children's programs of Title V of the Social Security Act, as amended in 1939."

In furtherance of this policy of the Academy, the chairman of the Committee on Legislation addressed a communication to the Honorable Robert L. Doughton, Chairman of the House Ways and Means Committee which had under consideration amendments to the Social Security Act. (See JOURNAL OF PEDIATRICS, September, 1946, p. 396.)

During cross-examination by Senator Pepper at the Senate hearings on S.1318, your chairman on legislation took occasion to urge upon the Senator the same line of approach as advocated by the Academy resolution quoted through a process of gentle "needling," having already experienced considerable needling himself at the hands of the Senator! The following passage-at-arms took place: (Senate hearings, page 84).

SENATOR PEPPER.—And you ought to be here begging us for funds that in any way whatever could be made available to provide for the children and the children-bearing mothers of this country. I think it does a disservice to your profession for you gentlemen to object or obstruct in any way the provisions of money that would help innocent children to live when otherwise they will die. I thank you very much.

DR. WALL.—We are begging it, Senator, and we are asking for extension of the Social Security Act for the very purposes which you now state, and I hope when that comes before the Senate, you will give it your support so that the Children's Bureau may be enabled to have more funds under Title V of the Social Security Act to care for the needs of those in need.

The Committee on Legislation would strongly urge that the proposal made by President Durand in his report to the Executive Board in June last be adopted by the Academy. Dr. Durand in speaking of the far-reaching results of the child health survey states: "I would suggest that a post-survey planning committee be named at our next meeting."

This suggestion was thoroughly discussed at a meeting of the survey committee in Washington on September 30 and October 1 and strongly supported by President-Elect Lee Forrest Hill. The consensus of the survey committee was quite unanimous that such a committee be named, not only to activate and implement the work of the survey, but to include in its functions advice and recommendations to the Executive Board and to the Academy as to the general policies of our organization, some of which by their very scope and extent prohibit detailed consideration at the busy semiannual meetings of the Board and at the annual meeting of the membership. "Policy Committee" was suggested as the title of such a committee.

The Committee on Legislation would also urge the formation of such a committee which would relieve our committee of the task of formulating the thought and opinion of the Academy on proposed legislation, which it now endeavors to interpret under the guidance of Academy discussions and expressions of views from the Executive Board.

A few members of the Academy—it must be emphasized that the word “few” is appropriate—have, through the written word and by oral statements, actually “out-Wallaced Wallace” in an effort to sabotage the efforts of the Legislative Committee to present to the best of their ability the policies of the Academy of Pediatrics. Should our committee, whose function it is to further or disapprove at the behest of the Academy matters of legislation pending in Congress, have the authority behind it of the opinions of a Policy Committee, the advice of which has in sequence been endorsed by the Executive Board and the Academy, our lot would not only be a happier one but the voice of the Committee on Legislation would be further strengthened.

In conclusion, I would express on behalf of the committee its deep appreciation of the cooperation of the state chairmen and of many of our members in the work at hand.

Respectfully submitted,  
JOSEPH S. WALL, Chairman  
W. L. CRAWFORD  
HARVEY F. GARRISON  
FRANK VAN SCHOICK

The report of the Committee on Legislation as given in person by Joseph S. Wall was accepted.

#### Report of the Program Committee

The Program Committee's work for the past year, as usual, consisted of the preparation of the program for the annual meeting. How successful it has been will be determined by the reaction of the membership to the program at the annual meeting.

Looking to the future, should the proposed redistricting become a fact, it is suggested that the spring meeting be largely devoted to the presentation of papers by members and others as has been the custom at regional meetings in the past. To arrange this type of program will require the cooperation of the membership in suggesting subjects and speakers.

Respectfully submitted,  
EDGAR E. MARTNER, Chairman  
FRANK H. DOUGLASS  
R. CANNON ELEY  
M. HINES ROBERTS  
MATTHEW WINTERS

The report was accepted.

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A Committee for Improvement of Child Health was voted largely for the purpose of interpreting the findings of the Child Health Survey but also to act as a policy committee to which questions of policy of the Academy could be referred. The committee consists of the following who were appointed by the President: James L. Wilson, Ann Arbor, Mich., Chairman; Arthur H. London, Jr., Durham, N. C.; Roger L. J. Kennedy, Rochester, Minn.; Clarence H. Webb, Shreveport, La.; H. G. Poncher, Chicago, Ill.; Hulda Thelander, San Francisco, Calif.; Grover F. Powers, New Haven, Conn.; George M. Wheatley, New York, N. Y.; and Warren R. Sisson, Boston, Mass.

The question of the Pan American Congress of Pediatrics was discussed extensively and plans were made for the cooperation of the various elements of the Academy in the promotion of this meeting.

#### Report of the Committee on Geographical Distribution of Pediatricians

The Committee on Geographical Distribution has been busy in a desultory way during the summer months. There are a few local surveys that are being completed to meet several requests that have come in, and I have written to several men to give them information which they have requested.

I am revising my survey of the Academy of Pediatrics to bring it up to date. I am also busy with maps to fit the proposed changes of regions of the Academy.

Respectfully submitted,  
OTTO L. GOEHLE, Chairman

The report was accepted.

#### Report of the Committee on Rheumatic Fever

Your committee, although holding no formal meeting since the Detroit session last year, has been actively engaged and has completed a revision of the statement, "Rheumatic Fever and the School Child." This is intended as a guide for school health authorities and is a combined contribution on the part of the Committee on School Health and the Committee on Rheumatic Fever. Emphasis has been placed on the diagnosis of rheumatic fever and not, as now exists, merely on the diagnosis of heart disease. The two committees feel strongly that the school offers an opportunity unparalleled for any other disease to provide the means for a frontal attack on rheumatic fever, and it is here that emphasis should be placed. They recommend: (1) that the school medical examination be improved to aid in more accurate recognition and supervision of children with rheumatic fever; (2) that more emphasis be placed on referral by teachers and nurses for medical review of pupils believed to be below par; (3) that less emphasis be placed on restricting the physical activity of rheumatic children and more attention given to daily observation of pupils for signs or conditions suggestive of rheumatic disease; (4) that there be available to school health services diagnostic and consultation service to aid in the diagnosis of rheumatic fever; and (5) that these services be developed in cooperation with and utilization made of existing medical and public health resources in the community.

Your Committee is now represented by three of its members on the American Council on Rheumatic Fever and has, through the Child Welfare Committee of the American Legion, stressed the importance of rheumatic fever as a public health problem. Two Research Fellowships established by the Legion have already been awarded. Several members of your Committee are members of the Advisory Committee for the Children's Bureau, and have attended meetings in Washington in May and September to discuss mutual problems. Rheumatic Fever programs have been set up in twenty states and more will be inaugurated as qualified personnel are available and standards met. The Academy Fellowship should again be reminded that it was through a recommendation of the Academy some eight years ago that children with rheumatic heart disease should be considered cripples and should, therefore, participate in funds allocated for crippled children under the Social Security Act. The program since that day has gone far in the care of these children and the Academy has played an important part in it.

Future objectives of your Committee are evaluation studies of programs already in operation for five years or more, studies in community planning and the setting up of registries in certain counties. The Academy's Child Health Study should provide, when completed, important information and valuable data for the future guidance of your committee, from which, it is hoped, that recommendations can be made.

Respectfully submitted,  
ALEXANDER T. MARTIN, Chairman  
STANLEY GIBSON  
JOHN P. HUBBARD  
HUGH McCULLOCH  
EUGENE H. SMITH  
R. R. STRUTHERS  
GEORGE M. WHEATLEY

The report of the Committee on Rheumatic Fever was accepted. Following the resignation of Alexander T. Martin, George M. Wheatley was appointed chairman of this committee.



## Report of the Committee on National Defense

The activities of the Committee on National Defense have been devoted entirely to the medical supervision of war orphans in cooperation with the United States Committee for the Care of the European Children.

This work had declined sharply since the earlier war period, but in May of this year we were notified that larger groups of children would enter this country under President Truman's directive of Dec. 23, 1945. Dr. Philip Stimson of our committee addressed the Pediatric Section of the New York Academy of Medicine with the object of obtaining a panel of Pediatricians to examine and care for these children, and the response was excellent.

The first children arrived in this country on May 20, 1946, and were admitted at two reception centers in the Borough of the Bronx. Between this time and July 27, seven groups totaling 265 children were examined. The children who entered the country this year differed radically from those of preceding years, since they now included those who had been liberated from concentration camps. It was obvious that the approach to the examinations and their conduct required more tact and patient understanding than with youngsters in the earlier groups. Every religious faith and all nationalities were represented.

Fortunately, many of the physicians were foreign born and could communicate with the children in their own language. Tuberculin and Schick tests could be carried out only after preparing the children and setting their minds at ease. In their past the hypodermic needle had been identified with pain, torture, experimentation, and extermination. Although examinations were limited to essentials, the aim was to be as thorough as possible because it was felt that ours was the responsibility for detecting serious abnormalities before the children made wide contacts in this country. For instance, of the 265 children, 145 had positive tuberculin reactions.

The variety of problems presented to the counseling staff and to the examining physicians resulted from the unusual experiences of these children. The only ones to survive the concentration camps were those who were told enough to work or clever enough to falsify their age or both. The case histories of the children are strikingly similar: Younger brothers and sisters, with their parents were killed—shot and gassed; the boys and girls have worked in munitions factories and coal mines at hard physical labor. They were old enough to be useful and to employ their wits to their best advantage. Though most of them had been in several of such infamous concentration camps as Dachau, Buchenwald, Theresienstadt, and Bergen-Belsen, a few had been in hiding for a while, until they too finally were apprehended. Obviously, only the physically fit and mentally alert survived. The inhuman and barbarous treatment to which these unfortunate children were subjected is beyond belief. The assortment of tortures that were practiced on them will remain indelibly seared in their minds and bodies and prove more lasting than the row of figures which had been burned into their flesh. The representatives of the "master race" for instance employed one child as a human target. Some children were mutilated in torture camps; one of the handsomest wears a very ugly red scar on his neck and face from the day when Nazis set a dog on him. One child survived experimental partial extirpation of the thyroid gland. Teeth constitute a special problem for most of the children. Almost all of them had at least one front tooth missing.

I am happy to report that whenever medical help was required it was readily obtainable; it was never questioned, and cooperation was always wholehearted. The pediatricians who made the routine examinations were always available for every medical contingency until the children left the Reception Center for other parts of the country. The service was entirely voluntary. We have gone beyond the membership of the American Academy of Pediatrics to obtain the services of specialists in various fields. Two roentgenologists, Drs. Sielman and Taterka have been x-raying children who were tuberculin positive; Dr. Eli H. Rubin has been consulted in the interpretation of chest roentgenograms; Dr. J. Burstan for electrocardiograms; and Dr. Jack Wolf in dermatological problems. More recently Dr. Walter Levy has been supervising the examinations and has been responsible for organizing teams of physicians

with the arrival of each new group. The following physicians have participated in this project and have been most cooperative: G. Alpert, J. B. Alter, Blazenstein, M. Blume, L. Budanz, Cohen, B. Denzer, A. Goldfarb, N. Gottschalck, L. Greenspan, N. M. Greenstein, H. Heidenheim, Landsmann, M. Loewy, Pasachoff, Prince, Robinson, G. Rook, A. Schwartz, Schweig, E. Siegel, Steinberg, S. Stone, Waltuch, H. Zweig.

The New York City Health Department has contributed freely of its facilities. The dispensary of the Lebanon Hospital which is near the Reception Center has provided generous assistance and in addition children have been cared for at the Morrisania Hospital, Lenox Hill, Willard Parker, and Beekman Street Hospitals.

Since completing this report, two additional groups of children have arrived in this country and their examinations are now being completed. It is possible that the data derived from the examinations may ultimately prove interesting and valuable should these children continue to arrive in increasing numbers.

Respectfully submitted,  
 CARL H. SMITH, Chairman  
 ROBERT A. BIER  
 CARL H. LAWS  
 RUSTIN MCINTOSH  
 DOUGLAS D. MARTIN  
 LENDON SNEDEKER  
 PHILIP M. STIMSON  
 JOSEPH STOKES, JR.

The report was accepted and the committee continued.

#### Report of the Committee on Postwar Courses in Pediatrics

Total number desiring refresher courses	24
Total number desiring residencies	225
Total	<u>249</u>
Number desiring refresher courses but have not been heard from	10
Number desiring residencies but have not been heard from	88
Total	<u>98</u>
Number desiring refresher courses on active list	14
Number desiring residencies on active list	137
Total	<u>151</u>

140 men have been placed in residencies.

26 men have been placed in refresher courses.

On Sept. 16, 1946, we circularized sixty hospitals. Forty-two hospitals have been heard from, offering a total of forty positions for 1947 and 1948. We have not circularized the hospitals for refresher courses as the demand is very small and the A. M. A. Journal has been publishing a sufficient list of postgraduate courses.

At the beginning of each month we try to publish a list of residencies and send this list to each man on our list. At the present time we have thirty-five men on our active list with whom we correspond continuously. We are trying to get these men placed and it is a difficult job. We sincerely hope that if any positions are open, we will be notified of them so that we may help these veterans find their places in pediatrics.

Respectfully submitted,  
 CLIFFORD G. GRULEE, Administrator

The report was accepted.

#### Report of the Committee on Tumor Registry

A meeting of the committee was held Sept. 25, 1946.

A preliminary report of the cases in the registry was made at the Round Table on Tumors, Benign and Malignant, at the Pittsburgh meeting, Nov. 13 to 16, 1946.

*Registration and Consultation.*—As of July 1, 1946, there were records of 573 cases of malignant tumors under investigation.

Seven new cases have been received for registration or consultation from sources other than Memorial Hospital since the April 29, 1946, report of this committee. The diagnoses were: malignant teratoma, liver; sarcoma, abdominal wall; osteoid osteoma; polycystic kidney; "fatigue" fracture; tuberculosis, osseous; constitutional inferiority.

The Children's Tumor Registry Exhibit has been completed. It was shown at the New York Academy of Medicine Graduate Fortnight on Tumor Oct. 7 to 18, 1946, and at the convention of the American Academy of Pediatrics, Pittsburgh, Pa., Nov. 13 to 16, 1946. An outline to accompany this exhibit explaining the purpose and procedures of the Registry has been prepared.

*Education.*—In accordance with the authorization of the Executive committee, June 12, 1946, a request was made of the Children's Bureau, of the United States Department of Labor to include a paragraph on the subject of Children's Tumors in that department's publications, *Infant Care* and *Your Child from One to Six*. A reply was received from Marion M. Crane, M.D., Assistant Director, Division of Research in Child Development on June 25, 1946, as follows:

Your letter of June 20th to Dr. Eliot has arrived while she is in New York acting as Vice-Chairman of the American Delegation to the International Health Conference. It will be called to her attention upon her return.

In the meantime I can assure you that in the next revisions of the Children's Bureau publications *Infant Care* and *Your Child from One to Six* the inclusion of paragraphs on the subject of neoplasms will be given full consideration in the light of the recommendations of the Academy and of the very interesting statistics that you have sent us.

It happens that both of these booklets have been completely revised quite recently, so it may not be possible to insert the additional material as soon as we would wish to.

The Children's Bureau is always glad to receive suggestions from the Academy as to ways in which we can make our publications more useful.

Several interviews were held with officers of the American Cancer Society. This national organization plans to include data from this Registry relating to children in their program of medical and lay education.

The following material is now available for graduate and undergraduate medical education and lay groups interested in the field of child health: children's tumor exhibit, statistical data, charts, and photographs.

This committee believes the facilities of the Registry would be further utilized by the medical profession if its existence were more widely known. It is recommended that the title and the address of the Registry be included (as formerly) in the JOURNAL OF PEDIATRICS on the page with the names of the Officers of the American Academy of Pediatrics.

Respectfully submitted,  
HAROLD W. DARGEON, Chairman  
HERBERT F. JACKSON  
HAYES MARTIN

The report was accepted.

#### Report of the American Board of Pediatrics

The members of the American Board of Pediatrics appointed by the American Academy of Pediatrics submit the following report of the work of this Board from Jan. 1, 1946, to Oct. 1, 1946.

During the spring and summer of this year we have held two oral examinations as follows: Cleveland, Ohio, April 27 and 28, 1946, and San Francisco, Calif., July 6 and 7, 1946. The mortality for the two examinations was 25.7 per cent which is 5.6 per cent lower than the mortality from October 1944 to January, 1946. This is a total drop of 18 per cent in the mortality since October, 1944, and we hope this will continue.

As you will notice, the Office of the Secretary has changed its address again and is now located at 1818 Twelfth Street, Des Moines, Iowa, and the telephone is 2-1572, listed under the name of Jerry O. Younglove. We hope this will be the last move for some time.

Because of difficulty with the engravers, our first Certificates in Allergy will not be issued until about October 15, but we hope to go along with this at a more rapid rate in the future.

Proof has been received from the A. N. Marquis Company on the Directory for Medical Specialists and we understand this is going to be off the press soon. We are attempting to obtain reprints of the geographical lists of the licentiates of this Board for distribution to licentiates, hospitals, and teaching institutions, but have had no definite word on this.

There has been no change in the personnel of this board, but Dr. D. J. McCune was re-elected to membership by the American Pediatric Society for a period of six years.

The committee set up to consider the special cases of returning veterans is still functioning. We are, also, cooperating with the Council on Medical Education and Hospitals of the A. M. A. in extending temporary approval to hospitals for residency training, pending official inspection by the Council. We hope this will make more training positions available to veterans in a short space of time.

Since our last report, the application fee for the examinations in pediatrics has been raised from \$75.00 to \$100.00, effective May 1, 1946. This may have to be increased even more in the future due to the high price of securing adequate secretarial help that is so necessary since the volume of correspondence and work has far exceeded anything we have ever anticipated.

Dates of the spring oral examinations have not been set. We are holding two oral examinations this fall; the first in Pittsburgh on November 10, 11, and 12, 1946, immediately preceding the Annual Meeting of the American Academy of Pediatrics, and the second in Boston on December 13, 14, and 15, 1946.

Respectfully submitted,

LEE F. HILL

HUGH MCCULLOCH

HAROLD C. STUART

The report was accepted.

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No reports were received from the following:

Committee on Honorary Fellows

Committee on Hospitals and Dispensaries

Committee on Immunization and Therapeutic Procedures for Acute Infections Diseases

Committee on Medical Education

Committee on Nursing Education

Committee on Pan-American Scholarships

Committee on Pediatric Awards

Committee on Mothers' Milk Bureaus

Committee on Nutrition

#### Report of the Committee on Cooperation With Nonmedical Groups

The Committee has been assembling data from its members and some state chairmen on methods of contacting lay groups interested in child care problems. The Medical Advisory Committee of the National Girl Scouts has submitted a brochure on "Directions to Camp Leaders" for review and suggestions in order to obtain the approval of the Academy. This has been revised by the committee and will be submitted to the Executive Committee of the Academy.

A second printing with a few revisions has been made of the Academy's camp card. Over 100,000 cards have been printed. An attempt will be made in the spring to put them in the hands of all pediatricians in order to standardize the camp examination.

At present the script "When Bobby Goes to School" is being revised to bring this picture up to date. During the last year there has been an increasing demand to show this picture.

Several national organizations interested in children have submitted questions to the committee which have been answered by the chairman.

Respectfully submitted,  
 ALBERT D. KAISER, Chairman  
 ROGER L. J. KENNEDY  
 MARVIN ISRAEL  
 JOSEPH I. LINDE  
 MARGARET NICHOLSON  
 JAMES C. OVERALL  
 WARREN R. SISSON  
 LILLIAN R. SMITH  
 EDWIN T. WYMAN

The report of the Committee on Cooperation with Nonmedical Groups was made by Albert D. Kaiser in Person with Mr. A. L. Rose present. There was some discussion of revising the film "When Bobby Goes to School," also of the Health Examination cards and their distribution, as well as cooperation with several different organizations such as the Girl Scouts and the Boy Scouts. The committee report was accepted.

#### Report of the Committee on Mental Health

Arrangements have been practically completed for the production of the motion picture on mental growth during the first two years. We hope it will be completed within six months.

Respectfully submitted,  
 BERT I. BEVERLY, Chairman  
 C. ANDERSON ALDRICH  
 FREDERICK H. ALLEN  
 BRONSON CROTHERS  
 GEORGE J. MOHR  
 ARTHUR H. PARMELEE  
 VICTOR E. STORK

The report of the Committee on Mental Health was discussed at length by Bert I. Beverly, and Mr. Heineman and Mr. Papineau of Pet Milk Company. It was decided to urge that company to complete the film which has been developed under the direction of the Committee on Mental Health. The report was accepted.

#### Report of the Committee on a Library and Museum of Pediatrics

The committee on establishing a pediatric library and museum has been stimulated by the offer of fifteen thousand (\$15,000.00) dollars by Mead Johnson & Company to start a building fund to house such a project.

At the present, the committee is exploring the field of libraries in an effort to learn how such a library can best serve the Academy and pediatricians.

It welcomes suggestions from members as to the need for such a library and how such needs can best be met.

The establishment of such a library is an undertaking of considerable magnitude, and the committee wishes to be fully informed before making recommendations to the Executive Board and the membership of the Academy.

Respectfully submitted,  
 EDGAR E. MARTNER, Chairman  
 ALBERT D. KAISER  
 HUGH MCGULLOCH

The Committee on a Library and Museum of Pediatrics was reported on by Dr. Edgar E. Martmer and after some discussion it was decided that the Executive Board approves having a permanent home and library, the funds to be raised in any manner possible and that Dr. Martmer be given a sum not to exceed \$500.00 to cover initial investigation. A generous offer with respect to the funding of such a building was received from Mr. Rose of Mead Johnson and Company.

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Dr. Hill brought up the question of representation of pediatricians on the Committees of the National Institute of Health. There are apparently sixteen different groups and not a single pediatrician on any group. Dr. Hill was empowered to write a letter in the name of the Academy requesting representation.

The question of pending legislation at the National level was discussed by Mr. Thomas Hendricks, Secretary of the Council on Medical Service of the A. M. A. and Mrs. Shuler, Supervisor of the Bureau of Information of the A. M. A., in some detail. Dr. Wall joined in in this discussion as did some members of the Executive Board. It was decided to approach the House of Delegates and ask them to give their approval to an expressed desire for cooperation between the A. M. A., and the American Academy of Pediatrics on legislation affecting the children in this country. It was voted that the Executive Board would be pleased to have one of its representatives present at the meeting which is held with representatives of the A. M. A. and Senator Taft and his group to make available what information the Academy may have on child care for the use of the Senatorial Group.

#### Report of the Committee on Cooperation With the American Legion

Efforts are being made to further the liaison work with the American Legion along two lines: (1) reorganize the personnel of the Academy who are assigned to this liaison work in such a manner that each state will have an active and energetic state liaison officer who will work in close cooperation with the American Legion child welfare representative of the state, and (2) formulate a practical program for future activity.

With regard to the first objective, reorganization of personnel involved in this work, a list is being obtained of the American Academy of Pediatrics members who were in the armed services during this war. An attempt will be made to interest as many of these men as possible in the various states to assume the duties of state liaison officers. Sixty per cent of the membership of the American Legion is now composed of veterans of World War II. It is felt that the younger members of the Academy should participate more actively in the work of the Academy. In addition, it is felt advisable that Academy veterans of this war be associated with the work of the present Regional Liaison Officers. In summary, the first step should be the careful and complete reorganization of personnel so that men who are actively interested in furthering this work will be appointed to the various positions, and those who either do not have enough time to do the work or who are not interested in it sufficiently can be dropped.

With regard to formulating a program for the future, the undersigned held a meeting with the Director of the National Child Welfare Division of the American Legion and her assistants in Indianapolis on September 15. A most satisfactory conference was achieved. On the night of September 15, another conference was held with the same personnel. Dr. Edward Clay Mitchell, of Memphis, Honorary Chief Liaison Officer, was present at the second meeting and contributed materially to the development of ideas for a future program. Mr. Jack Cann, editor of *The Legionnaire*, was present at the second conference and promised to publish in this paper, which is mailed to the homes of 3,750,000 legionnaires throughout the country, a series of articles on child welfare and health which are to be written by outstanding pediatricians of the country. The titles of the articles to be written and the names of the men who are to be requested to write these articles are now under consideration and will be taken up at the National meeting in Pittsburgh in November. The articles will be less than 1,500 words long, written for lay persons, and will emphasize important aspects of

child welfare and health. Several other possible projects were discussed, but it was decided to do one thing at a time and to concentrate on the production of these articles, which were promised in the past but have not been delivered.

It is worth emphasizing that the American Legion is a very powerful national organization with a membership of 3,750,000, that it has a very able and active director of the National Child Welfare Division, that it has the necessary financial backing to be of great assistance in the improvement of child welfare throughout the country, and that the child welfare personnel in the national office of the legion is very congenial and friendly toward the American Academy of Pediatrics. From these facts it would appear that a rare opportunity exists for the American Academy of Pediatrics, working with the child welfare division of the American Legion, to achieve a great deal of good for the children of America. Nothing worth while can possibly be obtained along these lines unless the members of the Academy of Pediatrics who are requested to help in this work do so with enthusiasm and interest and carry out their responsibilities in the most effective manner.

Respectfully submitted,

JAMES G. HUGHES, Chairman and Chief Liaison Officer  
EDWARD C. MITCHELL, Honorary Chief Liaison Officer  
LAWRENCE F. RICHDORF, Associate Liaison Officer  
EDWIN T. WYMAN, Area A Liaison Officer  
PRESTON A. MCLENDON, Area B Liaison Officer  
GEORGE M. LYON, Area C Liaison Officer  
JULIUS H. HESS, Area D Liaison Officer  
CLIFFORD SWEET, Area E Liaison Officer

The report of the Committee on Cooperation with the American Legion was given by James G. Hughes in person. This report was accepted and after much discussion Dr. Hughes was asked to formulate ideas for further cooperation with the American Legion and to present them later to the Executive Board. It was moved and carried that the Academy request that a pediatrician be put on the Medical Advisory Committee of the American Legion.

#### Report of the Nominating Committee

##### *Recommendations.—*

For Vice-President (President-elect):

John A. Toomey, Cleveland, Ohio

If the redistricting is *not* passed by the members:

For Chairman of Region IV:

Vernon W. Spickard, Seattle, Washington

If the redistricting is passed by the members:

For District I, Oliver L. Stringfield, Stamford, Conn. (1 year).

For District II, Paul W. Beaven, Rochester, N. Y. (2 years).

For District III, Philip S. Barba, Philadelphia, Pa. (3 years).

For District IV, Warren W. Quillian, Miami (Coral Gables), Fla. (1 year).

For District V, James W. Bruce, Louisville, Ky. (2 years).

For District VI, George F. Munns, Winnetka, Ill. (3 years).

For District VII, Thomas J. McElhenney, Austin, Tex. (1 year).

For District VIII, Vernon W. Spickard, Seattle, Wash. (2 years).

For District IX, The representative will be determined by a vote of the Latin-American members at the meeting of the Pan-American Congress in Washington, July 10 to 13, 1947 (3 years).

Respectfully submitted,

EDWARD B. SHAW, Chairman  
PRESTON A. MCLENDON  
HOWARD J. MORRISON  
WYMAN C. C. COLE

# The Academy Study of Child Health Services

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Dear Dr. Veeder:

It has become customary for a monthly report to be submitted to the JOURNAL OF PEDIATRICS by the Executive Staff of the Study of Child Health Services. During recent weeks, or, more accurately, months, the measure of our progress has been the number of drafts of a preliminary report of the pilot study in North Carolina that have been written, revised, discarded, and rewritten. The pressure of activity has been such that I have no formal report to present at this time. Perhaps you would consider it appropriate to publish this letter lest the impression be gained that the executive staff has paused in its progress toward the goal of completing the whole study at the earliest possible date. The truth of the matter is that the lights from our new offices on Massachusetts Avenue have been burning day and night and our whole staff has been busy grinding down the North Carolina data into tables, charts and maps.

At present writing a preliminary draft of the statistical analysis of the North Carolina material has been prepared for submission to the Executive Board of the Academy, the Committee for the Study of Child Health Services, and the Advisory Committee, and for distribution to state chairmen and the North Carolina Pediatric Society. This preliminary draft has been prepared for a twofold purpose: first, to give to state chairmen a preview of the amount and type of information which will be available for all States; and second, so that the committee appointed by the North Carolina Pediatric Society to draw up a final report may select from the formidable array of tabulated material those items which appear important for local planning.

Most of the state chairmen will be familiar with the tables which are included in this draft. These tables constitute a revision of the table forms which were discussed in detail last fall at the regional meetings held in Chicago, San Francisco, and Washington. The data for North Carolina have been entered in these tables and described in detail with the hope that state chairmen will find in this preliminary draft some help in anticipating a report for their own States.

It has not been considered a function of the executive staff to concern itself with recommendations arising from the facts which the Study has revealed in North Carolina. This is a responsibility which belongs to the duly appointed committee which, we hope, will reduce the overwhelming mass of factual data to more appropriate dimensions, as well as prepare the recommendations to serve as a basis for a continuing action program.

It is premature at the present time to quote any of the data presented in the preliminary draft. However, it is permissible to indicate at least the sort of questions to which answers are now appearing for North Carolina. First, a composite picture of the total volume of medical care rendered to the children of the state was obtained to show broad comparisons between areas of differing population, geographic and socioeconomic characteristics. The details of this composite picture were then examined more closely. The number and distribution of physicians and dentists and the extent to which they concentrate in urban areas in North Carolina have been described with the help of State maps. Particular attention has been given to the proportion of medical care and health supervision given to children by general practitioners, specialists and community health agencies. A detailed analysis has been made of hospital care, including all general hospitals which admit children, those which admit maternity cases in order to cover newborn care, and special hospitals, such as communicable disease hospitals, tuberculosis sanatoriums, nervous and mental institutions, and convalescent homes.

It is fair to state that the information now available should serve as a basis for the development of sound plans for the improvement of child health services in North Carolina.

Sincerely yours,

(Signed) JOHN P. HUBBARD.



## The Social Aspects of Medicine

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In the April, 1946, number of the JOURNAL OF PEDIATRICS (28: 503, 1946) is an article by Prof. A. Lichtenstein of Sweden, giving an outline of the Swedish system of medical care. In the letter from Dr. Donald Paterson appearing in the March, 1947, issue of this journal, reference was made to an article by Dr. Arvid Wallgren appearing in the December, 1946, issue of the *Canadian Medical Association Journal* (55: 605, 1946), describing in detail the education of physicians in Sweden and their various functions and roles in the general plan for medical care. The viewpoint of Dr. Wallgren, that primarily of the physician concerned, and the subject matter of this article are so different from Professor Lichtenstein's that it has seemed advisable to reprint Dr. Wallgren's article here. Obviously the Swedish system of medical care is the result to date of a gradual indigenous growth and development. It obviously cannot be transplanted in toto to our soil any more than can the English constitution. Nevertheless, it has more importance for us than the system of any other country, for in it private practice and State medicine exist all mixed up together, and its general management and control are in the hands of the leading physicians of the country.

If we are to escape from a complete governmental control of medical care, such as would result if the Wagner-Murray-Dingell Bill or legislation of that kind were passed, or from a situation such as is about to be imposed by the Labor Government on the medical profession in England, it will be because we physicians come forward with a constructive program meeting the basic medical needs. These needs are provision for the care of the medically indigent and for medical service in those areas of the country, chiefly rural, where physicians are lacking under the present hit-and-miss system of distribution of physicians. Any program of medical care which will meet these requirements must include Federal and State participation; in other words, what we physicians must do in order to retain the present system of private practice is to supplement it with some form of state-financed medicine, which we ourselves must devise if we are to control its operation. In the Maryland Plan, presented by Dr. Dean W. Roberts in this column (27: 384, 1945), this necessity was recognized, when with the support of the Medical and Chirurgical Faculty of the State of Maryland, the Legislature was asked for money to be used under the direction of the State Board of Health for the care of the medically indigent.

Sweden is a small country, and the Swedish plan may be looked on by us as a pilot experiment which has been conducted along democratic lines in spite of State participation, and which has worked excellently there from both the medical and lay points of view; therefore we can learn much from it even if we cannot copy it in detail. Perhaps its most important feature for us is that in Sweden a mixed system has been eminently satisfactory and successful to the lay public and the profession alike.

Dr. James Wilson in his article in this column (28: 231, 1946) has emphasized the importance of improving the education of physicians in this country as well as increasing their total number. It is interesting to note how much more thorough the Swedish system of education of physicians is than ours. The long years of training are made possible only through State aid to the medical student and later to the young physician while he is still in process of preparation.

## SOME ASPECTS OF THE MEDICAL PROFESSION IN SWEDEN\*

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### MEDICAL EDUCATION

WHEN the Swedish youth has finished his gymnasium, at which time he is about 19 years of age, and if he intends to study medicine, he has three different medical schools to choose between; the Universities at Uppsala and Lund and the Carolinian Medico-Surgical Institute in Stockholm. The number of students that can be accepted at the beginning of the courses twice a year is limited, 25 at each of the universities and 50 in Stockholm, thus 200 medical students annually. This limitation is partly due to the desire to facilitate the teaching, which aims as far as possible at individual instruction in Sweden, the maxim followed being that the fewer the students the more they learn, and partly due to a wish to produce no more than the required number of physicians. The result of this limitation of the number of medical students accepted is that there is usually fairly severe competition among them; those students who have had the best examination results at the gymnasium, which in general means those who are most ambitious and gifted, are selected. Medical students generally can thus be regarded as a picked group with good intellectual prerequisites to become good physicians.

The medical studies are divided into two separate stages, the pre-clinical and the clinical. The former lasts about  $2\frac{1}{2}$  to 3 years, the latter  $3\frac{1}{2}$  to 4 years. The student must pass the preclinical examination before he is allowed to attend the clinical classes. During the clinical course he is expected to acquire sufficient practical training to enable him to diagnose and treat patients. After qualifying, he must apply to the State Board of Health for a license to practise medicine. Almost every physician in Sweden endeavours to obtain additional clinical training by serving as an intern for some years after passing his qualifying examination. If he wants to become a specialist he has to study his special field of medicine by practising as an intern for at least 3 years. In addition to his practitioner's license he then has to apply to the Swedish Medical Association for a license as a specialist. There are very strictly regulated requirements for each special field.

One may differentiate between three kinds of physicians in Sweden, *viz.*, the hospital physician, the health officer, and the private practitioner.

*The Hospital Physician.*—The rapid advance of medical science has compelled an ever-increasing number of physicians to specialize, a development which is making itself apparent also in the hospitals. The hospital system is in a high state of development in Sweden, service of the highest class being given free of cost or at an extremely low charge. Patients pay, as a rule, 2 Swedish

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crowns a day in the public wards and 10 crowns for a private room, this charge being inclusive.\* The state or municipality, or the board of the province, is responsible for the covering of all other costs. The total daily costs at a Swedish hospital amount as a rule to 10 to 20 crowns for each bed. With few exceptions the hospitals are either state-run or under communal government.

From an administrative point of view, Sweden is divided into 24 Districts (Provinces), and in the capital city of each Province there is a central hospital with various special departments each with its head physician; in addition to this there are a number of smaller hospitals in the other towns. At the present time, the central hospitals in general are equipped with the following special services, *viz.*, departments of internal medicine, surgery, and radiology, an ear, nose, throat, and eye service, and departments of pædiatrics and of obstetrics and gynæcology. The ultimate aim is to establish also departments of psychiatry and of dermatology, wards for epidemic diseases, and laboratories for medico-physical research. The tuberculosis hospitals are run as separate units having no connection with the central hospitals, but the administrative system is the same. For surgical tuberculosis patients there are a number of State hospitals. Hospitals for the mentally ill are as a rule run by the State, only the leading cities having their own large mental hospital. The care of crippled patients is also a State service, four hospitals for cripples being at present in existence.

The head physician of a hospital is responsible for all activities being carried on in the different departments. He is paid for half-time services and has the right to carry on a private practice in addition to his work as a hospital physician. In most cases the head physician has his private reception rooms at the hospital, which places its premises, instruments, and staff at his disposal for a small fee. At some of the hospitals the hospital physician has the right to decide himself what fees he will take, at others he must follow a scale of charges approved by the General Board of the Provinces and the Swedish Medical Association.

The head physician is bound to treat without special charge all patients at the hospital and in his own department. He controls the admission of the patients and he alone has the right to judge which patients will be admitted. In some hospitals the head physician is permitted to accept a certain fee from patients in private rooms on condition that this fee is offered him, but he may not request payment. At other hospitals this extra income for the head physician is replaced by a certain increase in his annual salary. The social position of the hospital physician is among the highest in the community, his financial situation is satisfactory, and his living standard good. He is appointed from among many applicants by the King's cabinet, the State Board of Health serving as adviser. The Provinces have relatively small possibility of carrying their own candidates in the election of hospital physicians.

In addition to the head physician, all larger hospitals or hospital departments have an associate head physician who has the same salary as the interns but is responsible for part of the hospital activities, has the right to private prac-

\*A Swedish crown or krona is equivalent to 28c in Canadian funds.

tice, and can remain in this position for a longer time than the interns. He must have had special training in the particular field in which he specializes at the hospital and he is appointed by the State Board of Health on the recommendation of the head physician and the board of the hospital. This associate head physician deputizes for the head physician and is in charge of the hospital during his absence. It is from among these associates that the future head physicians are recruited. This arrangement with associate head physicians allows the work of the hospital to continue undisturbed, and the head physician is thus relieved of part of his burden. Associate head physicians have an income from salary and private fees, permitting him to raise a family without undue financial worry.

The interns are all full-time paid and are not entitled to carry on a private practice outside of the hospital. They receive about 9,000 Swedish crowns a year in addition to living quarters or a housing allowance, and their financial position is such that they can marry and raise a family. The intern serves as a rule for 3 years or more, but the period of internship is as far as possible limited to 3 years, in order to give a larger number of new graduates an opportunity to receive hospital training. At the present time, the competition for the majority of these internships is severe. The interns are appointed by the Board of Health of the Province.

*The health officers* working in the service of the State or the municipality and not attached to the hospitals are responsible for the health of the population in the district or town assigned to them. The State health officers receive for their services an annual salary of, on an average, 9,000 crowns and a pension. They are bound to treat patients for a fee approved by the State, which is lower than that received by private practitioners in general and slightly less than the health insurance rates. These officers are also obliged to visit patients in their homes for a certain fixed fee. Another part of their duties is to place their services, against extra compensation, at the disposal of tuberculosis dispensaries, welfare centres for children and expectant mothers, and schools, and to perform vaccinations against smallpox and other infectious diseases. It is also their duty to take charge of patients during epidemics in their district, and to visit, for no extra charge except their travelling expenses, various parts of their district where their presence may be required for investigating the possible cause of epidemics or insanitary conditions reported to the authorities. In each Province there is a chief health officer who is at the head of the other health officers of the Province and has the final say in all health questions in that area. He has a higher salary than the State health officer, and he has very little time for private practice.

There are about 400 State health officers in Sweden at present, but as the field of activity widens and the responsibility becomes too burdensome for one physician the larger districts are being divided, and it is expected that about 300 new posts as health officer will be made available during the next few years. The number of inhabitants in the district of a health officer varies at present from about 2,000 to about 17,000 persons. The financial position of the State

health officer is satisfactory and his standard of living good. The competition for these posts is fairly severe. Until quite recently, health officers have, if anything, been overqualified as regards medical training; it is not unusual to find men with 10 to 12 years of training at different hospital departments behind them, and their medical knowledge is as a rule on a high level. State health officers retire on a pension at 63 years of age.

In the cities, the municipal health officers correspond to the State health officers in the Provinces; in the smaller cities there is only one of these officers, in the larger ones there is a chief municipal health officer who in some instances is full-time paid, and district municipal health officers who are part-time paid like the State health officers and have medical duties and a social position corresponding to those of the latter. Although the annual salary is usually much lower than the State health officer's their incomes are nevertheless good. They are not compelled to keep to any particular scale of charges but in all probability they calculate their fees in most cases to fit in with health insurance rates. They are entitled to a pension, generally 6,000 crowns at 65 years of age.

Some of the district municipal health officers act as medical advisers for the staff of industrial establishments, government offices and institutions, transport concerns, schools and dispensaries, and to organizations for the welfare of mothers and children and municipal child welfare centres. The municipal health officers are appointed by the city board, and in most cases are highly qualified physicians with good incomes and a satisfactory standard of living, and favourable social standing.

The chief municipal health officer in the leading cities does not carry on any medical activities and is not permitted to have a private practice. His work is entirely administrative, and he acts as adviser to the city board. His annual salary amounts to about 20,000 crowns, and when certain paid commissions which more or less automatically fall to his lot to perform are added, his yearly income amounts on an average to about 25,000 to 30,000 crowns.

The head of the central tuberculosis dispensary of the district can also be classed as the same type of physician as the chief health officer. He must be a specialist in tuberculosis, and he is in charge of anti-tuberculosis campaigns in his district. He is half-time paid and can have a private practice. Under him he has local tuberculosis dispensary physicians who are provincial and municipal health officers. All cases of tuberculosis must be reported to the tuberculosis dispensary, which, through its health nurses and physicians, arranges for the inspection of the patient's home environment and sees to it that he receives the necessary medical attention. Tuberculin tests and x-ray examinations (in the case of tuberculin-positive patients) are carried out at the laboratory of the central tuberculosis dispensary. The local tuberculosis dispensary physician receives a certain annual sum for his work.

Besides the position as chief municipal health officer there are a few other research, laboratory, and administrative posts in the kingdom requiring a full-time medical officer such as, for instance, the post of medical superintendent at various scientific institutions and at the different departments of the State

board of health; head medical adviser of schools in some of the leading cities; chief medical superintendent in the various branches of the defence forces; and a few positions in the social services. The total salary, including benefits allowed, amounts on an average to about 25,000 crowns a year. The Swedish Medical Association has strongly opposed every attempt to introduce the fixed total salary principle for physicians doing practical work, such as hospital physicians, and hitherto they have succeeded in carrying their point. It remains to be seen whether this policy can be maintained in the long run in the face of the ever-hardening insistence of the public on full-time paid physicians.

*The Private Practitioner.*—The third category of physicians in Sweden is the private practitioner. The number of these is small in comparison with other types of physicians. They are mainly to be found in cities and towns, rarely in rural districts. Although the private practitioners are in the main dependent on the income they make from their practice, the majority of them nevertheless have some form of regular annual income from service at various government or private institutions or business concerns. This extra income is probably large enough, in most cases, to cover the rent for living quarters and reception rooms.

The private practitioner's fees are not subject to any fixed rates but are wholly determined by the confidence of the public in the physician in question. If his fame is wide and his reception rooms well-filled the fee can be raised, while conversely, and if there is much competition with other physicians in the district, he must be content with smaller fees, especially at the beginning of his career as a practitioner. The income of some of the private practitioners is therefore low to begin with, and it is not unusual to find physicians of this category in the larger cities whose medical activities show a loss for the first few years.

The private practitioners have in most cases acquired good training subsequent to their medical studies, and a great many of them are specialists. In some branches of medicine, such as pædiatrics, the demand for private practitioners is so great that they can count on a satisfactory income right from the start of their career. In a few exceptional cases they have their own private clinic, where they treat their patients, admit maternity cases, perform operations and so on. In the leading cities there are also private donation hospitals, to which any physician may remit cases and where he may treat his own patient and charge him the fee he considers adequate.

It is among the private practitioners that the widest variations are found with respect to income, living standard, and social position. Some of these physicians, in these respects at any rate, can be compared with hospital physicians and clinical university professors, the majority are on a level with, or slightly lower than the health officers, and some are in a less satisfactory position from several points of view.

Relatively few physicians start their career with the idea of becoming a private practitioner, in spite of the fact that this form of the profession offers the freest scope. Most of them strive to obtain a hospital appointment or a post as a health officer, thus providing a greater degree of security not only during the years when they are able to work, and in case of illness, because a

certain minimum income is guaranteed under all circumstances, but also for their old age, by ensuring a pension. The private practitioner must protect himself against possible loss of income through illness by costly insurance premiums, and he also has to arrange for his own pension.

#### THE PHYSICIAN AND THE HEALTH INSURANCE FUNDS

There are no physicians in Sweden appointed specially to treat patients belonging to health insurance funds. There is complete freedom as regards the choice of physician, and a person with a health insurance is at liberty to consult any qualified physician, including specialists, he desires. Either the patient pays the fee to the physician and then applies to the sick relief fund for payment, against production of the physician's receipt, of the amount which the Fund allows in accordance with the rate fixed by the Government for the examination and the treatment the patient has received; or the physician sends the Fund a bill for the amount which is due to him according to the same rate. In some cases, as for instance when a specialist has been consulted, the amount allowed by the Fund is lower than what the patient has paid, but as a rule the fee requested by the physician is more or less on a level with the sick benefit. The sick relief fund fixes a certain fee for the first consultation in the physician's consulting room (5 crowns) and for subsequent consultations (3 to 4 crowns); it fixes the fee for a visit to the patient's home, the amount (8 to 20 crowns or more) varying with the distance (8 to 30 kilometres or more) the physician has to travel; and it also fixes a certain additional fee (2 to 20 crowns) for various special examinations and surgical interventions, the rate for each type of examination or operation being specified. On the whole, physicians seem to be satisfied with the sick relief rates; this can also be seen from the fact that the rates approved by the head physicians of the hospitals diverge only very slightly from the rates of the health insurance companies. The rates followed by the State medical health officers are slightly lower than the sick relief rates. The members of the insurance funds are also satisfied with the insurance regulations, as they are at liberty to consult whatever physician they please. At the present time, more than 50 per cent of the Swedish population are entitled to sick benefits, and a proposal has been submitted to Parliament that a bill be passed compelling all Swedish citizens to become members of a health insurance fund.

#### THE STATE BOARD OF HEALTH

There is no Ministry of Health in the Swedish Cabinet. The part of the health services not connected with university instruction is bound up with the social organism; the university hospitals form part of the ecclesiastical administration. The executive and controlling body of the social administration in the matter of health questions is the State Board of Health, the head of which, or director general, is a trained physician who has under him the heads of various departments (*e.g.* hygiene, hospitals, health officers, veterinary medicine, pharmacy, administration) who are often full-time paid physicians. By their side they have a scientific advisory board, consisting of professors belonging to

the medical schools and in different branches of medicine to whom they can refer more complicated medical questions for deliberation and advice.

The State board of health has many different tasks, but I shall only mention here some of the most important of them and those concerning the activities of the medical profession; the granting and cancelling of practitioners' licences; receiving and judging complaints against physicians; offering suggestions in connection with the selection of hospital physicians and health officers appointed by the Government; consenting to and approving of new posts of this type; examining and giving consent to architects' designs for hospitals; issuing regulations regarding health questions; control of all matters concerned with the combating of epidemics in the kingdom; supervising and saying the final word in all questions of public health and the care of the sick; dealing with medicinal problems and the affairs of veterinary medicine; and assisting the courts in making pronouncements on questions of a medico-legal nature. The care of mental defectives is entirely a Government concern under the management of the State Board of Health. For the performance of scientific investigations the medical board has at its disposal a bacteriological, a chemico-legal, and a pharmaceutical laboratory as well as an establishment devoted to veterinary bacteriology. The State Board of Health works in intimate co-operation with the State Institute for Public Health.

*The Swedish Medical Association.*—This Association is comprised of 96 per cent of all Swedish physicians. It has an executive committee which holds meetings once a week. The measures taken by this committee are examined by the Board of the Association, which meets as a rule at least four times a year, and which makes the final decision in the more important matters pertaining to the Association. Once a year there is an assembly of the Association, to which representatives are sent from the local medical unions in different parts of the country. The Association has done an enormous amount to improve the financial position of Swedish physicians, and its members are bound to abide by the decisions of the executive committee or the Board. No agreement may be finally settled, and no appointment applied for, without the consent of the Board or the executive committee. When the conditions are unduly bad and unacceptable to the Association the post is not advertised in the *Journal of the Swedish Medical Association*, which is equivalent to announcing that it may not be applied for until the conditions have been approved. This happens time after time, the result being that negotiations are opened up between the representative authorized to act for the Association and those offering the post in question, and in practically every case the outcome is an improvement in the conditions. The position of the Association in this respect is a very strong one, and the discipline among its members good.

The fixing of standards for the training of specialists, and investigating the applications of individual physicians for a specialist's licence, forms an important part of the work of the Association. A high moral and ethical standard among the members of the Association is aimed at by control of their activities through the local medical unions and by criticism and punishment of delinquents. The member's fee is at present 100 crowns a year.



Different categories of physicians are united into professional associations which are included as unions of specialists in the Swedish Medical Association. These professional Associations safeguard the social and financial interests of their members in collaboration with the mother Association. One of these professional associations is the Association of Young Physicians, which comprises nearly one-half of all the Swedish medical men.

#### MEDICAL SCIENTIFIC SOCIETIES

Good provision has been made for the interchange of scientific ideas among physicians. The Swedish Medical Society, which includes among its members the majority of the physicians in the kingdom, holds a meeting in Stockholm once a week. The city of Gothenburg and the university towns, Lund and Uppsala, also have their own medical societies, and each capital city in the Provinces where there is a central hospital has its own local scientific union holding meetings regularly. The various special branches of medicine have their own societies which are regarded as sections of the Medical Society; they have meetings usually once a month. There are two medical journals published in the Swedish language, the *Journal of the Swedish Medical Association*, and *Nordisk Medicin*, the latter being the organ of the Medical Society. In addition to these there are the *Uppsala Läkareförenings förhandlingar* and the different *Acta* journals (*Medica*, *Chirurgica*, *Pædiatrica*, *Oto-Laryngologica*, and so on). Once a year, in November, physicians assemble for an annual meeting, the Parliament of Physicians, lasting for three days, at which professional questions and scientific problems are discussed.

The contact between Swedish physicians and their colleagues in the other northern countries is a lively one. *Nordisk Medicin* accepts articles from all the Scandinavian countries in the language of each particular country, the *Acta* publications are shared by all the northern countries in common, and at regular intervals of two to three years congresses are held alternately in the different northern capitals on various branches of medicine. An ever-widening exchange of teachers and students is taking place. No physician with a degree and a licence from one northern country is, however, allowed to practise in any of the other countries.

Postgraduate training is arranged for through annual courses subsidized by the State, which are held in Stockholm and Gothenburg, and in addition to these there are special courses for school physicians, health officers, and other such categories at varying intervals.

# Academy News and Notes

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## NOTICE

Due to the increased cost of running the *American Board of Pediatrics*, the board has found it necessary to raise the application fee to \$125.00, effective May 1, 1947.

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## DEATHS

William Ewing Sinclair of Orlando, Fla., died Dec. 29, 1946.

Charles E. Turcot, of Quebec, Que., died Jan. 8, 1947.

James LeRoy Fester, of Pittsburgh, Pa., died Jan. 16, 1947.

Justin Allis Garvin, Shaker Heights, Ohio, died Dec. 7, 1946.

Ralph E. Pray of Salinas, Calif., died Dec. 18, 1946.

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Dr. Harold W. Buchner of Oklahoma City is now the State Chairman for Oklahoma.

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Dr. Frazier Binns of Nashville, Tennessee, has been released from service in the Army.

Dr. R. R. Struthers, Montreal, Que., has been released from UNRRA service.

## Comment

### WOMEN AND CHILDREN AND WAR

Three articles showing the effect of war on women and children appear in this issue of the JOURNAL. They were not accepted for publication with any thought of propaganda, but purely for their scientific value. One describes conditions at Leningrad during the siege by the Axis armies; another, what happened at Budapest when the tables were turned and the Russians overran Hungary; the third, the effect on Holland when the Dutch resistance movement reacted to the German occupation. In the January number there is a brief reference to the effects of the atomic bomb on children in the article by Agerty on Japanese pediatrics.

These reports of what happens to infants and children under conditions of modern warfare give food for thought. It is true our own country was at war, but in the light of what happens in countries where the actual fighting takes place, we had no hardships. In fact, we in the United States as a nation have little realization of what war really means. Let us contrast with these records the infant mortality rate for the United States during the war years.

<i>Year</i>	<i>Infant Mortality Rate</i>
1941	45.3
1942	40.4
1943	40.4
1944	39.8
1945	38.3

At this point we leave the reader to his own thoughts.

We hope no one will infer that the lowering of the infant mortality rate in the United States during the war years shown in the above statistics was due to the EMIO program. We raise this point as this inference will undoubtedly be made by those furthering such proposals as the Pepper Bill of the last Congress. Such an inference is intellectually dishonest. So far there has never been produced the slightest evidence to show that the infants of enlisted men who received medical care paid for by the Federal government had a lower mortality rate than infants without such benefits, or that the medical care they received was better than that of infants in general. There were a number of other happenings that took place in the field of health and medical care coincident with this fall in the infant mortality rate during the war years. Among these were a marked decrease in the number of physicians available for civilian medical care, a rise in the venereal rate, in Missouri, at least, an increase in the number of infants under the care of osteopaths, a decrease in the consumption of sugar and fats, gasoline and travel restrictions, preventing vacations and picnics, an increase of women in industry. Take your choice and ride your own hobby. In recent weeks, during the cold weather, having sweated over the bedside in a number of homes with the temperature around 80° F., we have been toying with the idea that the decrease might have some connection with the fuel shortage and restrictions during the war years which prevented the overheating of American homes.

The decrease that took place is the continuation of a cycle that started many years ago and is due to many factors. One of these is the result of the improvement in the education of the public in health matters, but basically it is due to the tremendous developments which have taken place in medical education and science.

B. S. V.

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## Original Communications

### THIO-URACIL IN CHILDHOOD HYPERTHYROIDISM

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FROM the viewpoint of the pediatrician, hyperthyroidism in children has always been regarded as a primary medical problem. As a result, each new case is granted a thorough medical trial in the hopeful expectancy of an arrested disease process; inadequacy of these regimens is attested to by the proportion of hyperthyroid children who come to thyroidectomy. With the demonstrated effectiveness of thio-uracil, in controlling the symptoms of adult hyperthyroidism, pediatric management of the disease is worthy of further consideration.

Hyperthyroidism occurs infrequently in children. Bram,<sup>10</sup> in a series of 1,200 cases of thyroid disease in childhood, reported 0.8 per cent as hyperthyroidism. In a comparable study of exophthalmic goiter in all age groups, he reported 2.5 per cent as being in children. Somewhat more than 1.0 per cent of 15,500 cases at the Mayo Clinic occurred in children of 14 years or less. In a series of 13,200 cases of hyperthyroidism at the Crile Clinic, only forty-two cases were observed in children of this age group. Since 1922, at Children's hospital, twenty cases have had the considered diagnosis of hyperthyroidism.

The course of childhood hyperthyroidism may be benign or severe and acute. While the disease develops more rapidly in children than in adults, it is usually a relatively milder form. Reilly<sup>9</sup> indicates the tendency for multiple cycles of the disease, with succeeding cycles becoming less severe, but without total remission until full arrest occurs. It is these relatively benign cases with a tendency for self-remission which prove amenable to medical management. The development of hyperthyroidism in the adolescent child poses the additional problem and possibility of amelioration of thyrotoxic symptoms when the adolescent crisis is past. Because of the importance of the thyroid hormone in the normal development of the child, most investigators and all pediatric literature agree that each case warrants a thorough medical trial before surgery is considered.

From the Milwaukee Children's Hospital.

Medical treatment is preferably along conservative lines. In the initial stages of the disease, complete physical and mental rest are necessary, in so far as possible. Gradually increased patient contacts and interests are allowed, as governed by the clinical course of the patient. A general high-caloric, high-vitamin content diet is given, but all stimulants such as cocoa and the cola drinks are avoided. Discernible infectious foci are to be noted, with correction when the patient's condition permits. The importance of the thyroid gland as sequentially implicated in a constitutional neuroendocrine dysfunction is particularly stressed by Bram,<sup>10</sup> who advocates psychotherapy as a valuable adjunct in treatment. Understanding and cooperation of the patient's family forms the basis of this adjustment on the part of the patient.

In addition to these general measures, many and varied drugs have been used with the hope of symptomatic or specific relief. Of these, iodine is of proved value in a small percentage of cases. Phenobarbital and other barbiturates, quinine, insulin, and prostigmine all have had their advocates. Now, the use of thio-uracil, propyl thio-uracil, and radioactive iodine offers further possibility of medical management of the disease. It is to be emphasized that because of the tendency for spontaneous remissions of the disease process in children, the results of any form of therapy are necessarily guarded.

The writers have had the privilege of using thio-uracil in six cases of childhood hyperthyroidism. Case summaries to date follow:

#### CASE REPORTS

CASE 1.—B. R., a white girl aged 10, was admitted to Children's hospital Aug. 22, 1945, with a chief complaint of diarrhea that had not responded to treatment. The present illness dated to February, 1945, at which time a persistent diarrhea, accompanied by an elevated afternoon body temperature was present. Five to seven soft stools were passed daily, without accompanying digestive upset. In spite of vigorous symptomatic treatment, following cessation of therapy the disturbance recurred. For three months previous to admission, there had been weekly episodes of epistaxis. The mother stated that she had noticed a "rapid heart-beat" for about one year. There had been a weight loss of indeterminate amount, and the mother noted the child had become "thinner about the face." There were no complaints related to the neuromuscular system. Past medical history revealed only the usual childhood diseases. The maternal grandmother had "goiter," and symptoms of thyroid disturbance. Four siblings were living and well.

The patient was a thin, well-developed white female of the stated age, whose quickness of action drew immediate attention. The eyes were somewhat prominent, but there were no eye signs or exophthalmos present. The tonsils were enlarged and mildly reddened. The thyroid gland was palpably enlarged, without nodularity. The precordial rate was 90 to 120 beats per minute, and the precordial impulse was characterized as "strong and forceful." There were no murmurs. Examination of the lungs and abdomen was negative. Blood pressure was 110/50. There was a noticeable tremor of the extended hands, but the quadriceps test was not elicited. The patient weighed 24.1 kg. The child was placed on bed rest while laboratory procedures were pending.

On laboratory examination, catheterized urine specimens were sterile. Repeated stool examinations showed normal intestinal flora, and no evidence of parasitism. Blood agglutination tests for the typhoid-paratyphoid-dysentery organisms were negative. Blood counts were within normal limits, and the Kline test was negative. A tuberculin intradermal test with 0.01 mg. tuberculin was negative.

During the first week of hospital care, the patient had two or three formed stools daily, but a yellowish mucoid discharge exuded from the rectum almost constantly. This was of insufficient quantity to require the wearing of an absorbent pad. There was a low-grade afternoon fever present. On August 30, a blood cholesterol value was 245 mg. per cent. X-ray film of the wrists showed a bone age identical with the chronological age. A basal metabolic rate determination on August 30, was plus 26 per cent and plus 29 per cent. When no clinical improvement was noted following another ten days of inactivity, the patient was given thio-uracil in a dosage of 0.2 Gm. daily. At this time she weighed 24.5 kg. There was no immediate discernible change, although on September 11, the basal metabolic rate determination had fallen to plus 14 per cent. During the next month, however, she gained weight steadily to 28.6 kg.; her blood pressure averaged about 115/75, and she was less overly active. The frequency and consistency of the stools approached normal. The pulse remained extremely variable. On October 13, another basal metabolic rate determination was minus 9 per cent. Accordingly, she was discharged to the outpatient department on October 16, with instruction to take 0.1 Gm. of thio-uracil daily. She was asked to return at weekly intervals for progress examinations.

Inability to supply the medication necessitated a three-week interval when thio-uracil was not given. Because of this, she was asked to re-enter the hospital on Nov. 26, 1945. The parents stated that diarrhea was no longer a complaint, and that her behavior was more calm. They had noted a transient swelling in the thyroid area, although the gland seemed unchanged in size on examination. The pulse rate was 160 beats per minute, and the paper tremor of the extended hands was more evident. On November 27, basal metabolic rate determination was plus 28 per cent. The blood cholesterol was 221 mg. per cent. An electrocardiogram taken at this time showed only a sinus tachycardia of 150 beats per minute. On November 28, thio-uracil, in a dosage of 0.4 Gm. daily, was begun, together with phenobarbital in a dosage of 0.016 Gm. three times daily. Within one week the pulse rate steadied at 100 beats per minute. On December 13, another basal metabolic rate determination was plus 3 per cent. The patient was discharged the following day on a maintenance dosage of thio-uracil, 0.2 Gm. daily, and 0.032 Gm. of phenobarbital daily.

Bi-weekly clinic visits were continued. She gained weight slowly. The thyroid gland could no longer be palpated at the end of the third month. On March 26, 1946, a basal metabolic rate determination was minus 2 per cent, and the thio-uracil dosage was reduced to 0.1 Gm. daily. Her excellent health continued, and she was able to tolerate a return to school. On July 25, 1946 the basal metabolic rate determination was plus 8 per cent, and the thio-uracil dosage was reduced to 0.05 Gm. daily. At present the pulse rate averages 85 beats per minute. On November 9, the determination was minus 8 per cent. Thio-uracil was discontinued on this date. Blood pressure is 110/70. The child weighs 31.8 kg., and in all respects is developing and behaving normally. A minimal tremor of the extended hands and the need for monthly clinic check-ups are the only present evidence of her once active thyroid disturbance.

CASE 2.—J. P., a white female aged 14 years, was admitted to Children's hospital Sept. 17, 1945, because of an injury to the right elbow following a fall. She was the ward of a children's home where she had been considered a behavior problem because of emotional instability and "nervousness." She had always been thin-faced and was unable to gain weight normally. There were no gastrointestinal or cardiorespiratory symptoms, and menstruation was not established.

The maternal grandmother had required a thyroidectomy, and for reasons unknown, a tracheotomy had been performed two years later. Past medical history revealed a previous fracture of the same elbow in 1940, but was otherwise irrelevant.

On physical examination the child was apprehensive, and complained bitterly about any movement. She was well developed and fairly well nourished, weighing 48.6 kg. A diffuse enlargement of the thyroid gland was noted. There was no bruit. No exophthalmos or eye signs were present. There was a fine tremor of the extended left hand. There was a painful

swollen deformity at the right elbow, with marked limitation of motion. Cardiorespiratory and neuromuscular systems showed no abnormality.

Roentgenologic examination of the elbow showed a deformity due to previous fracture, and a recent fracture of the proximal end of the radius with angulation. Urinalysis was normal, the Kline test was negative, and the sedimentation rate and blood cholesterol values (203 mg. per cent) were within normal limits.

On September 18, under general anesthesia, an open reduction and excision of the radial head was carried out, and a cast was applied. The convalescence was uneventful, and on September 28, the cast was removed, and physical therapy initiated. During this period, frequent examinations by a series of examiners had directed the child's attention to her thyroid gland, and the unfortunate connotation of her grandmother's experiences was brought to mind. This in no way allayed her symptoms. Initial basal metabolic rate determination was made September 29, and two tests averaged at plus 25 per cent. Although the factors of the healing fracture and recent psychological disturbances were considered, a tentative diagnosis of hyperthyroidism was made, and thio-uracil in a dosage of 0.1 Gm. twice daily was begun.

She was continued on this dosage for two weeks, at which time the basal metabolic rate determination was unchanged; the dosage was then increased to 0.4 Gm. daily. During the subsequent two-week period, she gained 2 kg. weight, and was less emotional. A basal metabolic rate determination on November 1, 1945 showed a slight decrease to plus 23 per cent, and the child was discharged to the outpatient clinics on a maintenance dosage of 0.2 Gm. thio-uracil daily. Weekly white blood cell counts were taken. No immediate additional changes in the physical condition were apparent.

During the period following hospital discharge until May 15, 1946, she did not take thio-uracil with regularity, difficulties with her supervisor leading her to "even-up" by destroying the pills. On March 15, 1946, a basal metabolic rate determination was plus 37 per cent. At this time her symptomatology was much the same as on initial admission. In June, 1946, she again came under the care of her parent and was persuaded to follow a regular schedule. Accordingly, she was readmitted to Children's hospital to be regulated on another course of thio-uracil.

On this admission history of May 15, the mother noted that the patient had frequent "excitable fits" and "crying spells." The tremor of her hands was more marked, and the thyroid gland was unchanged in size. Her weight at this time was 51.0 kg., and the pulse rate averaged 110-120 beats per minute. A basal metabolic rate determination on May 16 was plus 37 per cent. Two white blood cell counts averaged 6,700 cells with about 39 per cent neutrophilic forms. She was given 0.4 Gm. thio-uracil daily. Blood counts were taken twice weekly during early regulation. On May 27 another determination was plus 27 per cent. At this time the patient weighed 52.7 kg., and her mannerisms and emotional behavior were uniform. Accordingly, she was discharged to her parents on a maintenance dosage of 0.2 Gm. thio-uracil daily. Arrangements were made for her family physician to take weekly blood counts, and she was asked to report any illness or untoward symptoms to him immediately.

She was seen in the outpatient clinic July 5, at which time she weighed 55.0 kg. Her pulse rate averaged 110, but no traces of jittery behavior existed. On August 8, she was hospitalized overnight for laboratory procedures. Basal metabolic rate determination averaged plus 8.5 per cent. The patient weighed 55.0 kg. at this time. Thio-uracil dosage was reduced to 0.1 Gm. daily for two weeks, and since, she has been maintained on 0.05 Gm. daily. She has continued in excellent health.

CASE 3.—C. B., a white girl aged 10 years, was initially seen in the outpatient department of Children's Hospital Feb. 20, 1946. The referring physician had made the tentative diagnosis of early chorea, chiefly on the basis of a "pounding heart." Questioning revealed that during the previous three weeks the patient had been "nervous" and cried easily without adequate cause. She also had "palpitations of the heart." When seen by her physician, she was advised to try absolute bed rest and phenobarbital sedation for two weeks. When,

during this time, she had no symptomatic improvement. she was sent to Children's hospital. She entered the hospital March 11, 1946. Previous to the onset of the presenting symptoms the child had been quiet and unemotional. There were no complaints referable to the gastrointestinal or neuromuscular systems. Family history and past medical history were non-contributory, although the mother admitted to "nervous exhaustion" several years previously. There was no familial history of thyroid disease.

Physical examination showed a well-developed and well-nourished child, who had atypical choreiform movements of the extremities. There was no exophthalmos. Tonsils were huge and cryptic. There was a diffuse enlargement of the thyroid gland; no bruit was audible. There was a soft systolic precordial murmur without thrill. A fine tremor of the extended hands was evident. Blood pressure was 120/50. Pulse rate was 90 to 110 per minute. Weight was 31.8 kg.

The patient was placed on absolute bed rest while diagnostic studies were pending. The sedimentation rate was 4-9-24 (normal 5-10-25), the Kline test was negative, and complete blood counts were within normal limits. An electrocardiogram taken March 11 was within normal limits, as was an orthodiagram of the same date. A chest x-ray film showed questionable enlargement of hilar glands on the right side. A tuberculin test with 0.01 mg. tuberculin was negative. The cardiology consultant, in evaluating the heart murmur, expressed the opinion that it was not due to an active carditis. The pulse rate varied from 90 to 129 beats per minute, and an afternoon fever of 99.5 to 100° F. was present. When, after two weeks of enforced inactivity and in the presence of an excellent appetite, the patient lost 1.5 kg. of weight, attention was redirected toward the thyroid gland. On March 26, a blood cholesterol determination was 165 mg. per cent. The basal metabolic rate determination on March 26 was plus 24 per cent and plus 21 per cent.

On March 27, phenobarbital in a dosage of 0.016 Gm. three times daily was started. No improvement was noted after one week, so on April 7 the patient was placed on thio-uracil in a dosage of 0.1 Gm. three times daily. During the following week the patient regained her entrance weight, but the hyperactivity was undiminished, and the pulse and body temperature curves were unchanged. A basal metabolic rate determination on April 21 was minus 3 per cent. On April 22, the thio-uracil dosage was reduced to a maintenance level of 0.1 Gm. daily, and she was discharged to the out-patient clinics, with instructions to return at biweekly intervals.

On the fourth return visit, May 6, the mother related that for ten days previously the child had limped on the left leg as evident on examination. There was a slight restriction of internal rotation at the left hip, and an area of tenderness over the inferior ramus of the left pubic bone. A tentative diagnosis of osteochondritis of this area was made, and the patient was hospitalized for observation. In addition to the localizing findings, the child still had a tremor of the extended hands and tongue, quick nervous movements, and a tachycardia with a forceful precordial impulse. A basal metabolic rate determination at this time was plus 17 per cent. Pelvic x-ray studies showed no bony abnormalities. The child was placed on complete bed rest, and thio-uracil dosage was increased to 0.2 Gm. daily.

On May 12, sudden pyrexia initiated the onset of acute follicular tonsillitis. The infectious process precipitated an agitated state similar to that seen on initial admission. Choreiform movements, constant lip-licking and protrusion of the tongue, and a throat culture that revealed numerous streptococcal forms again made chorea a strong possibility. Electrocardiographic studies were again normal, as was the sedimentation rate. Under penicillin therapy the throat findings resolved rapidly, and she was allowed full activity May 21, 1946. She was discharged from the orthopedic service to the outpatient clinics on June 6.

Another basal metabolism rate determination June 16 was plus 12 per cent. Thio-uracil was reduced to 0.15 Gm. daily. During this period she gained weight to 33.6 kg., and the mother felt that the child was more quiet than at any time since the onset of symptoms. On August 7, a basal metabolic rate was minus 7 per cent, and the thio-uracil was reduced to 0.05 Gm. daily. Since this time she has shown only a slight tremor of the extended hands, the goiter has regressed in size, and she has gained weight to 36.3 kg. The blood



pressure averages 95/65, and the pulse rate is 75 to 80 beats per minute. Thio-uracil medication was discontinued Sept. 20, 1946. Future program calls for early tonsillectomy and continued observation at monthly intervals.

CASE 4.—M. R., a white girl aged 13 years, was admitted to Children's hospital on April 2, 1946, with the chief complaint of "bulging eyes" of two weeks' duration. The mother had always felt that the child had a tendency to be nervous, but recently this had become more apparent, and the child had become emotionally labile. She had lost an unknown amount of weight, in spite of a voracious appetite. She was always tired and lacked the stamina of her siblings. There were no cardiorespiratory or gastrointestinal symptoms. Menstruation was not established.



Fig. 1.—Case 4. Appearance after four months' thio-uracil therapy.

The past medical history was noncontributory. Familial history of thyroid disturbance was present in the maternal grandmother, and one sister.

Physical examination showed a lanky, thin, but well-developed girl who darted quick glances about her. She responded to directions with overly rapid movements, and fidgeted on the examining table. There was a moderate degree of exophthalmos, and a definite lid-lag was present on looking down. No bruit was audible over the eyeballs or thyroid gland. The pulse rate was 100 per minute, and the blood pressure was 130/50. The thyroid gland was barely palpable, firm, and without nodularity. There was a fine tremor of the extended hands and protruded tongue. Examination of the cardiorespiratory and neuromuscular systems was essentially negative. The weight was 34.5 kg.

Laboratory studies revealed a blood cholesterol value of 194 mg. per cent, a negative Kline test, and a sedimentation rate of 3-9-20. After two days of bed rest, the basal metabolic rate determination was plus 25 per cent and plus 20 per cent on two readings.

Following admission to the hospital, and while studies were obtained, she was put on bed rest, and her activity was limited as much as possible. Thio-uracil in a dosage of 0.3 Gm. daily was begun on April 5. After one week's time the patient seemed better adjusted to hospital routine, and was able to rest more completely. The tremor of the hands became less obvious. On April 19, a basal metabolic rate determination was plus 15 per cent. The following day the dosage of thio-uracil was increased to 0.4 Gm. daily. At the end of the subsequent two weeks the pulse rate remained at a lower level, and the patient had gained weight to 39.9 kg. She was allowed gradually increasing activity at this time in preparation

for discharge. Another basal metabolic rate determination on May 1 showed a level of plus 8 per cent. She felt well, and was discharged to the outpatient clinics May 3 on a maintenance dosage of 0.2 Gm. thio uracil daily.

The patient was followed in the laboratory at biweekly intervals, and examined at the end of two months. At this time the activity was perceptibly diminished, the exophthalmos was less, and the blood pressure was 120/75. When next seen on July 27, the basal metabolic rate determination was minus 2 per cent, and the patient weighed 42.3 kg. The thio-uracil dosage was reduced to 0.15 Gm. daily. When seen Sept. 14, the weight had increased to 44.1 kg. No signs of thyrotoxic activity were noted. Subsequently, thio uracil dosage was decreased gradually to 0.05 Gm. on alternate days. On Nov. 2, 1946, the basal metabolic rate determination was plus 8 per cent. Thio-uracil was discontinued on this date.

On subsequent biweekly checkups, the patient has continued in good health. Observation will continue at monthly intervals.

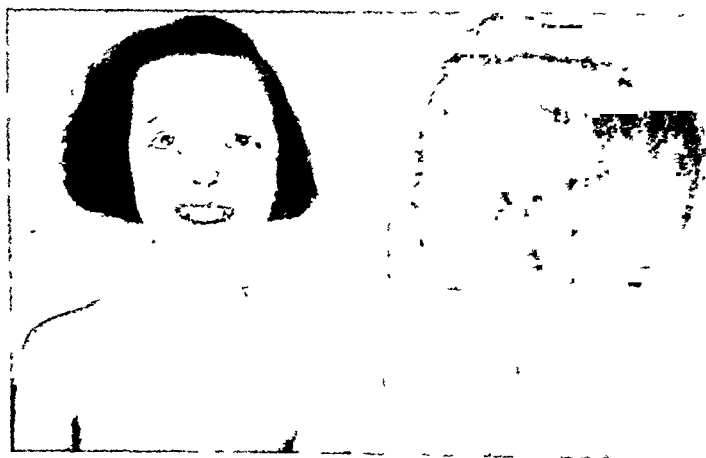


Fig. 2.—Case 5. Appearance before treatment.

CASE 5.—M. S.,\* a 9 year-old white girl, had a swelling of the neck for one month previous to admission to Children's hospital on June 26, 1946. This caused the child no discomfort, but had been noticeably enlarging. The neighbors had thought "her eyes were sticking out," and had mentioned this to the family. Because of this, the mother had consulted her physician. Questioning revealed that despite a ravenous appetite, the child had become steadily more thin, the amount of weight loss being unknown. For six weeks previously she had been very emotional and nervous. Although she had been regarded as "high-strung—we all are," this tendency was now pronounced. No symptoms referable to the gastrointestinal, cardiorespiratory, or neuromuscular systems could be ascertained. There was no familial history of thyroid disturbance. On June 24, a basal metabolic rate determination done at a private laboratory was plus 41 per cent. Hospitalization was advised.

Physical examination on June 26 revealed an alert, skinny child with marked bilateral exophthalmos. She was apprehensive, and jumped or was startled at any extraneous sound. Her hair was fine and silky. Exophthalmos was prominent, and lid-lag and "quick-look" were present. There was anterior fullness of the lower neck, and the thyroid gland was smoothly and symmetrically enlarged, roughly 4 x 5 cm. The pulse rate was 140 beats per minute. The blood pressure was 140/40. A functional systolic murmur was present at the apex, and bruits were audible over the eyeballs and thyroid gland. The skin was noted to be warm, the palms and soles being moist. There was a fine tremor of the extended hands. No quadriceps weakness was noted. The patient weighed 23.5 kg.

\*Case of John Reynolds, M.D.

Urinalysis was normal, and the Kline test was negative. Blood cholesterol level was 162 mg. per cent. Wrist x-ray films for development of centers of ossification according to Todd, revealed the bone age to be slightly in excess of the chronological age. Two blood counts averaged 7,400 with 55 per cent neutrophilic forms.

On June 29, the patient was placed on thio-uracil, and was given 0.1 Gm. four times daily. At 4-day intervals, the white blood cell counts were 6,200, 5,500, and 4,400, with 38, 40, and 32 per cent neutrophilic forms, respectively. Accordingly, on July 8 the thio-uracil dosage was decreased to 0.2 Gm. daily. During this period the patient was allowed graduated activity from full bed rest to unlimited activity. She gained weight to 26.8 kg., the pulse rate was diminished to 110 beats per minute, the entrance symptom of jitteriness was lessened, and she was able to play quietly with other children. On July 9, 1946, a basal metabolic rate determination was plus 22 per cent. She felt well, and at the time of discharge, July 10, the white blood cell count was 6,500, with 35 per cent neutrophilic forms.

She was followed as an outpatient at biweekly intervals, and the blood counts remained at this level. On July 21, the thio-uracil dosage was reduced to 0.15 Gm. daily. She gained weight steadily to 27.7 kg., and the mother felt the eyes were less prominent. Her sleep was undisturbed, her appetite was excellent, and general health remained good. On August 14, the pulse averaged 100 beats per minute; the blood pressure was 130/75. The size of the thyroid gland was unchanged. The precordial murmur had disappeared, as had the bruits previously audible over the eyeballs and thyroid gland. Accordingly, the dosage of thio-uracil was reduced to 0.1 Gm. daily. On August 28, the white blood cell count was 6,500, and the neutrophilic forms had fallen to 24 per cent. With the reduction of thio-uracil to 0.05 Gm. daily, the count on Sept. 25, 1946 was 8,000, with 46 per cent neutrophils. Some return of thyrotoxic symptoms has recurred with this dosage, and increased dosage required for control of these symptoms has produced neutropenic tendencies. Therefore, she has been shifted to a corresponding dosage of propyl thio-uracil, and clinical and laboratory observation is continuing.

CASE 6.—P. K., a white girl aged 7 years, has been under the pediatric supervision of one of us (F. R. J.) since infancy. When seen in March, 1944, she had evidence of an acute upper respiratory infection. There was a moderate pharyngitis and cervical adenitis. Symptomatic treatment was given. A low-grade fever present at this time persisted after all other evidence of acute infection had disappeared. Sedimentation rates and complete blood counts at this time were within normal limits.

In June, 1944, she was again seen because of a persistence of this low-grade fever, and an additional complaint of "palpitations of the heart." The pulse rate ranged from 100 to 130 beats per minute, and had been noted to be increasingly rapid. Her eyes were noticeably prominent without true exophthalmos. There was a tremor of the extended hands. A soft systolic murmur was audible over the precordium, and the heart action was tumultuous. A definite thyroid enlargement was noted. Accordingly, a diagnosis of hyperthyroidism was entertained.

The patient was placed on bed rest at home, and was given 10 drops of Lugol's solution daily. A basal metabolic rate determination after two weeks of iodine therapy was plus 29 per cent. The thyroid gland was noticeably increased in size. On August 30, a basal metabolic rate determination was plus 26 per cent, and the blood cholesterol determination was 132 mg. per cent. Bed rest and iodine medication were continued. On Sept. 19, 1944, another basal metabolic rate determination was plus 21 per cent. On the following day, thio-uracil in a dosage of 0.1 Gm. three times daily was started. This dosage was decreased after two weeks to 0.2 Gm. daily, and further decreased after another two weeks to 0.1 Gm. daily. This dosage was continued for one month. On Oct. 17, 1944, a basal metabolic rate determination was plus 11 per cent, and the blood cholesterol determination was 185 mg. per cent. The pulse rate at this time averaged 95 beats per minute, and the complaint of palpitations was no longer present. The thio-uracil dosage was decreased to 0.05 Gm. daily, and remained so for four months, when it was discontinued. On November 28, the basal metabolic rate determination was plus 15 per cent; on Jan. 23, 1945, it was plus 11 per cent.

The systolic murmur was no longer audible, and the patient was allowed increased activity. On May 1, 1945, the basal metabolic rate determination was plus 12 per cent; on July 30, it was plus 13 per cent. It is to be emphasized that during this period the child carried on a fairly normal life with restrictions only from extremes.

On Dec. 15, 1945, the basal metabolic rate determination had risen to plus 20 per cent and although all physical and subjective evidences of thyrotoxicosis had disappeared, thio-uracil in a dosage of 0.15 Gm. daily was begun. On March 16, 1946, with the dosage of thio-uracil reduced to 0.05 Gm. on alternate days, the basal metabolic rate determination was plus 22 per cent. On June 22, after completion of two weeks of day camp activities entailing considerable excitement, it had risen to plus 38 per cent. The mother insisted the child had no aggravation of symptoms, and had remained quite calm. For the following week the thio-uracil dosage was again increased to 0.15 Gm. daily, and was then reduced to 0.05 Gm. daily. On August 14, the basal metabolic rate determination was plus 13 per cent.

At present, thio-uracil medication has been discontinued and the child allowed fairly normal activity. She is enjoying unrestricted school activities, and none of the original subjective or objective findings are evident. Observation at intervals will continue.

#### COMMENT

In this brief series, no notable reactions to the administration of thio-uracil have been observed. In Case 5, a moderate leucopenia could be controlled by reduction of drug dosage. It is felt that this case, unless shown to do well with propyl thio-uracil, will require thyroidectomy. Every case showed an eosinophilic blood reaction, reaching its peak about the sixth week of thio-uracil therapy, averaging about 15 per cent of the differential count. This proportion diminished slowly, but a relative eosinophilic increase persisted as long as thio-uracil therapy was continued. This is regarded as individual sensitization to thio-uracil.

There is no hard and fast rule by which termination of treatment can be predicted. Williams<sup>13</sup> concluded that except in a few cases in which there are toxic reactions to thio-uracil, the drug can be used indefinitely, and that as long as it is used, a remission of the disease is maintained. The recent excellent summarization of Beierwalthes and Sturgis<sup>3</sup> offers the opinion that thio-uracil therapy may be discontinued at the end of an average of ten months with the prospect that 60 to 80 per cent of patients will experience a relatively persistent remission of symptoms. Burke<sup>5</sup> reported a case in a female aged 10, in which drug-induced remission had persisted one year following twelve months of thio-uracil therapy. Bram,<sup>10</sup> in discussing medical treatment of childhood hyperthyroidism, believed that two consecutive normal basal metabolic rate determinations indicated at least temporary remission of thyroid overactivity. It is our practice to decrease or increase amounts of the drug given each patient on the basis of present requirements and previous response. Following this criterion, the patient in Case 1 has received the drug continuously for thirteen months, while the one in Case 3 was under thio-uracil therapy for but five months.

We are unable to evaluate these cases as to permanency of cure, since the period of observation has been too brief. However, these children while under treatment with thio-uracil and with restrictions from the extremes of physical and mental activity, have carried on reasonably normal lives. Exacerbation of symptoms while under stress has been readily controlled by treatment gauged to their

apparent needs. In the case of adolescent patients, it is felt that thio-uracil therapy might well cause the symptoms of hyperthyroidism to remain in remission until controlled by the establishment of the more stable period of adulthood. Though subtotal thyroidectomy may be required at one time, we feel that an advantage has been gained by retaining thyroid action at the time of the individual's greatest need, for future needs.

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## INFECTIOUS HEPATITIS IN CHILDHOOD

### A REPORT OF TWO INSTITUTIONAL OUTBREAKS AND A COMPARISON OF THE DISEASE IN ADULTS AND CHILDREN

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INFECTIOUS hepatitis (which is now believed to be the same disease as catarrhal jaundice) has long been recognized as occurring sporadically and in epidemic form in both civilian and military populations. During wartime it has been prevalent among troops, particularly in places where living quarters were crowded and sanitary conditions poor. In contrast, during peacetime it is said to be primarily a disease of childhood,<sup>1-4</sup> appearing either sporadically or in epidemics in schools, camps, and institutions. Family outbreaks involving several children are not uncommon. Blumer,<sup>2</sup> in reviewing fifty epidemics occurring before 1923, found that about 70 per cent of these involved the younger age group. In several outbreaks reported subsequently, 65 to 100 per cent of cases have occurred in children.<sup>3-10</sup> Because of certain inherent difficulties in investigating this disease, and also possibly because of its usually mild and apparently benign course in childhood, little attention was directed toward the juvenile type. But with the appearance of the more severe adult forms in soldiers, the military importance of infectious hepatitis became evident, and efforts were applied toward the elucidation of some of its fundamental problems. Recent investigations have resulted in certain new information on the etiologic agent,<sup>11</sup> its possible manner of spread,<sup>12, 13</sup> and its prevention.<sup>14-16</sup> Thus it has been shown in experiments employing human volunteers that the etiologic agent is filtrable and resistant to a temperature of 56° C. for thirty minutes. It is believed to be a virus. This agent is known to be present in the feces and blood of patients in the acute phase of disease, and there is experimental evidence that the intestinal-oral route may be of importance in its spread, since the disease may be produced in human volunteers by feeding infective feces.<sup>17-20</sup>

There is no reason to believe that infectious hepatitis, which has appeared in large outbreaks among troops during World War II, differs from catarrhal jaundice which appears sporadically or in outbreaks among children. Experimentally there is some support for this concept furnished by immunologic evidence which shows that adult human volunteers, convalescent from hepatitis induced by the administration of a strain of virus obtained from the feces of children with the disease in the United States, were immune when reinoculated with a strain of virus derived from the stool of a soldier in the acute phase of epidemic infectious hepatitis contracted in Sicily.\* Both strains of virus used in this

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\*Personal communication to W. P. H. from J. Stokes.

experiment also produced homologous immunity. Nevertheless, complete proof of the identity of the two diseases is lacking. This is due in part to lack of a satisfactory serologic test and susceptible laboratory animals. Experiments using human volunteers have been necessarily limited in number and therefore of limited statistical value. It has not been possible as yet to explore the occurrence of various strains of virus which may have distinct serologic characteristics. Until such investigations have been made, the identity of different outbreaks of infectious hepatitis caused by various strains of virus cannot be established.

As a result of the war experience with infectious hepatitis among troops, considerable data concerning clinical manifestations in adults have been accumulated<sup>21-25</sup> and it is evident that there are certain differences between the characteristics of the disease as it appears in adults and children. These differences are related principally to severity of the infection; inasmuch as they have thus far received little emphasis, it is the object of this paper to describe two epidemics of infectious hepatitis in children and to compare the clinical course of disease in children with that reported in adults.

#### CLINICAL MATERIAL AND METHODS

Two institutional outbreaks of infectious hepatitis were studied. In one, fifty-three cases of hepatitis with jaundice occurred, along with fifty-six cases of questionable hepatitis without icterus.\* A description of this epidemic and the use of gamma globulin as a prophylactic measure in the exposed population has appeared elsewhere.<sup>15</sup> In the other institution, sixty-eight patients developed hepatitis with jaundice; of these, forty-four (65 per cent) were children. In this report only those cases with jaundice and in the age group under 16 years will be considered. Since the two epidemics involved children of different types who are not comparable, the outbreaks will be described separately.

*Highland Heights.*—In November, 1944, infectious hepatitis appeared in a Catholic home for children in New Haven. The home is situated just beyond the central part of the city, and consists of one large building housing approximately 300 children and thirty-nine adults. At the time of the epidemic, 90 per cent of the children were between the ages of 6 and 16 years. During the period of November, 1944, to March, 1945, there were fifty-two cases of infectious hepatitis with jaundice among the 300 children, and a single case among the thirty-nine adults. In forty-four (84.6 per cent) children the clinical course could be divided into two phases: (a) a preicteric phase, from the onset of symptoms to the appearance of jaundice; and (b) an icteric phase, lasting until clinical jaundice disappeared. Eight children (15.4 per cent) had asymptomatic jaundice as the presenting complaint. In the typical case, the preicteric phase began abruptly with headache, fever, and gastrointestinal symptoms. Of the last, abdominal pain and vomiting were the most prominent, with anorexia and nausea occurring less frequently. In Table I are recorded the most commonly occurring symptoms in the preicteric phase in the Highland Heights children, with comparable tabulations for two groups of adults with infectious hepatitis.

\*Acknowledgment is made to Dr. Paul L. Boisvert for calling our attention to this outbreak, to Sister Mary Catherine Teresa and members of the staff at the St. Francis Orphan Asylum, and to Dr. Joseph D'Amico of New Haven, Conn., for their cooperation.

TABLE I. RELATIVE FREQUENCY OF PREICTERIC PHASE SYMPTOMS

SYMPTOMS	CHILDREN			ADULTS					
	44 INSTITUTIONAL CASES*			167 MILITARY CASES†			27 EXPERIMENTAL CASES‡		
	NO.		%	NO.		%	NO.		%
Anorexia	10		22	138		82	26		96
Nausea	10		22	126		75	16		59
Vomiting	23		52	55		33	6		22
Fever	24		54	90		53	27		100
Abdominal Pain	25		56	73		42	21		77
Headache	33		75	59		35	20		74

\*These are children in the Highland Heights outbreak.

†Figures taken from a clinical description of infectious hepatitis in American troops.<sup>21</sup>

‡These cases occurred in volunteers who were among those who served as subjects for the transmission of infectious hepatitis in experiments conducted by the Neurotropic Virus Disease Commission, United States Army.<sup>15, 22, 24</sup> The series is small but the experimental cases were studied with special care.

TABLE II. DURATION OF PREICTERIC AND ICTERIC PHASE AND FEVER IN THREE GROUPS OF PATIENTS WITH INFECTIOUS HEPATITIS

	PREICTERIC PHASE			ICTERIC PHASE			FEVER		
	NO.	DURA- TION (DAYS)	AVERAGE NO. DAYS	NO.	DURA- TION (DAYS)	AVERAGE NO. DAYS	NO.	DURA- TION (DAYS)	AVERAGE NO. DAYS
Children*	58	1-15	4.8	96	2-32	9.8	48	1-10	3.8
Military cases†	167	1-18	5	200	4-83	27	90	2-15	5.0
Experimental cases‡	27	2-21	7.2	27	8-31	20	27	4-14	7.9

\*Institutional cases in the Highland Heights and Southbury outbreaks.

†Same legends as Table I.

Among the children, diarrhea and constipation were rare, as were malaise, chills, and generalized aches and pains. Usual temperatures ranged from 99.6 to 101° or 102° F. but occasionally to as high as 105° F. (rectal), the highest temperature usually being at the onset of disease and declining during the ensuing four to five days of the preicteric phase to normal. The preicteric period averaged about five days, after which jaundice became evident. With the appearance of jaundice, a striking amelioration of symptoms occurred. The temperature remained normal, the gastrointestinal disturbances vanished, appetite was excellent, and the child felt quite well almost at once. All of the children were hospitalized in the institution infirmary until clinical jaundice disappeared. The duration of jaundice in the fifty-two children ranged from two to thirty-two days, averaging eleven days (Table II). There were no seriously ill patients in this outbreak. Complications were infrequent, consisting of atypical pneumonia in one child and generalized acute dermatitis in two children. One relapse occurred in a child two and one-half weeks after his discharge from the infirmary. The one adult who contracted the disease in this outbreak had a similar but more severe course than the average juvenile patient, with deeper and more prolonged jaundice and gastrointestinal symptoms.

**Southbury Training School.**—The second outbreak occurred at the Southbury Training School for the Feeble Minded, located in a rural setting near Southbury, Conn.\* This institution has an average patient population of 1,300,

\*Acknowledgment is made to Dr. Herman Yannet, medical director of the Southbury Training School, for his assistance and cooperation.

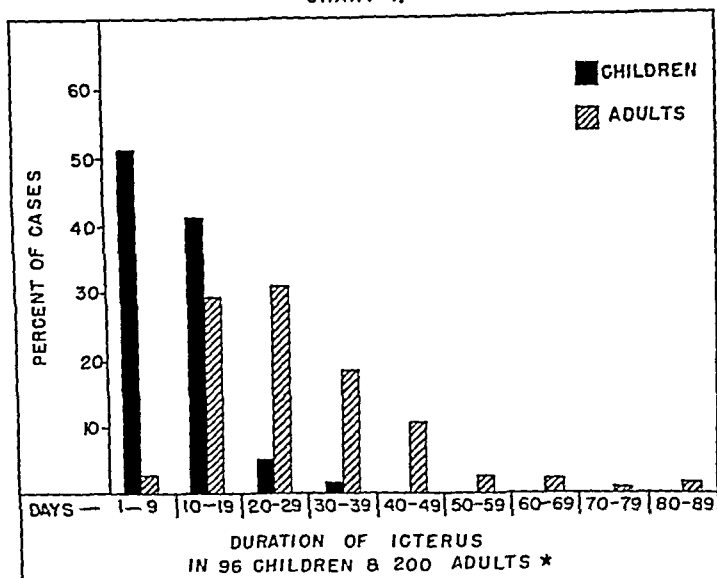


consisting of low, middle, and high-grade mental defectives housed in groups of twenty to eighty in separate cottages according to mental and chronological age. The chronological ages range between 5 and 65 years with the majority between 6 and 16 years.

In July, 1945, two cases of infectious hepatitis developed in a cottage for infirm patients, and during the next four months there were six cases scattered in several cottages. By the end of November, there was a sudden increase in cases in two adjacent cottages housing low-grade mentally defective boys, most of whom were bed ridden and incontinent of urine and feces. Forty of the one hundred sixty-seven patients in these two cottages developed infectious hepatitis with jaundice in the subsequent two months. At the same time, sixteen cases appeared among the remaining cottages. In all, sixty-eight cases of hepatitis with jaundice developed between July 10, 1945, and March 4, 1946. Forty-four (65 per cent) of these occurred in the age group under 16 years; eighteen (27 per cent) were between 16 and 25 years; and six (8 per cent) were 26 and over. The symptoms of the forty-four children to be described here differed from that of the Highland Heights patients, but the difference is probably more apparent than real. Since the Southbury group represents low-grade mental defectives for the most part, subjective symptoms could not possibly be elicited from the majority of patients, and only fourteen (32 per cent) are recorded, therefore, as having a preicteric phase, while in thirty (68 per cent) jaundice was the presenting symptom. In nine of the fourteen patients (64 per cent) who were known to be sick before the appearance of jaundice, fever and vomiting were the consistent abnormalities. In only three patients were subjective symptoms recorded: one complained of nausea, and two of headache. The fevers ranged from  $100^{\circ}$  to  $105^{\circ}$  (rectal), and, as with the group described previously, declined toward normal over a period of five days as the jaundice appeared. In a few patients, fever and vomiting persisted through the first day or two of jaundice. In forty-one (93 per cent), however, the icteric phase was completely asymptomatic. Jaundice was mild and persisted for an average of eight days with a range of three to twenty-one days. In only two patients were the elicited symptoms and signs suggestive of nonicteric hepatitis. Thirty-two patients were hospitalized, the length of hospital stay varying between one and twenty days, and averaging seven days.

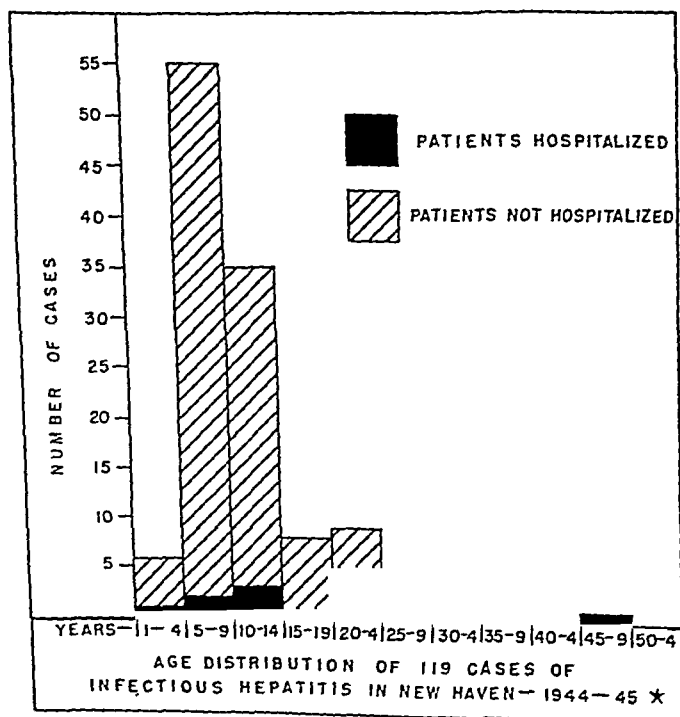
Laboratory work on the hospitalized group included the determination of the total number of leucocytes as well as examination of stained smears of the peripheral blood, examination of the urine for increase in bilirubin and urobilinogen, and determination of serum icterus index. Ordinarily the leucocyte count and icterus index were performed on admission to the institution hospital, so that only normal figures are recorded for a certain number of patients who subsequently developed obvious jaundice. Twelve patients had leucopenia, with less than 5,000 leucocytes per cubic millimeter; eighteen patients had between 5,000 and 10,000 leucocytes per cubic millimeter; only six patients had more than 10,000 white blood cells per cubic millimeter. Polymorphonuclear leucocytes numbered as few as 450 cells and lymphocytes as few as 400 cells per cubic millimeter during the period of leucopenia in certain patients in the

CHART 1.



\* Adult Cases Taken from Havens, W.P.—J.A.M.A.—126, 17-23, 1944

CHART 2.



\* HIGHLAND HEIGHTS CASES NOT INCLUDED

preicteric phase. Numerous atypical lymphocytes such as have been described in infectious hepatitis<sup>26-29</sup> appeared in the peripheral blood during the acute phase of the disease.

#### DISCUSSION

In this paper, attention has been directed to the concept that infectious hepatitis as it occurs in epidemic form among troops and catarrhal jaundice as it appears among children, are probably the same disease but differences in severity of clinical manifestations are evident (Chart 1). That the adult and childhood diseases are probably identical is suggested by the fact that in all civilian outbreaks in which adults and children are exposed, a certain number of cases occur in individuals over the age of 16 years. In New Haven, during the winter of 1944-1945, when the Highland Heights institutional outbreak occurred, 119 additional cases were reported in the city.\* Of these, only nineteen (16 per cent) were in individuals over 16 years of age. Chart 2 illustrates the age distribution of these cases, and calls attention to the fact that of the nineteen patients whose disease was serious enough to require hospitalization, thirteen (69 per cent) were in the adult group. Thus as in other civilian outbreaks, a certain number of cases occurred in adults, and the adults seemed to have a more severe disease.

The striking feature of the two outbreaks of infectious hepatitis among children described here was the mildness of symptoms and their short duration. Characteristically, by the time jaundice appeared these children felt well and it was difficult to keep them in bed. In contrast is the persistence of anorexia, nausea, abdominal discomfort, and often vomiting for eight to ten days in the adult case of average severity. These facts are in agreement with the findings of others.<sup>10, 30, 31</sup> Among the ninety-six children described here there were no examples of severe hepatitis with prolonged jaundice or protracted convalescence as have been reported frequently in adults and occasionally in children.<sup>1, 32</sup> In Chart 1 is compared the duration of icterus in the ninety-six children and 200 adults who represent military cases with infectious hepatitis in the Middle East. The majority of children in this series fall in the "mild disease" group. The highest icterus index reported for the Southbury group was forty-seven units, and in only six (6.3 per cent) of the total ninety-six patients comprising both groups of children did jaundice persist for more than nineteen days. There were no deaths from infectious hepatitis in the juvenile group.

Although it is possible that differences in severity of infectious hepatitis could be due to variations in virus strains, the observations reported here bear out what has been noted previously. Cockayne<sup>1</sup> in an early review of the disease pointed out that children, who are so prone to exhibit vomiting and diarrhea with any gastrointestinal disturbance, frequently have less marked symptoms of this kind with catarrhal jaundice than do adults. Cullinan<sup>31</sup> and Ford<sup>30</sup> have also noted the tendency for the disease to be more severe in adults than in children. In the one adult case in the Highland Heights outbreak and in the patients over 16 years of age in the Southbury group of cases, the icteric indices tended to be

\*We are indebted to Dr. Joseph I. Linde, Health Officer of New Haven, for the collection of data on cases occurring in the city.

higher and the duration of jaundice longer than in the children affected. However, although there were no severe cases among the children studied in these two outbreaks such cases do occur, and examples of prolonged jaundice with relapses and even death have been reported in children.<sup>1, 22</sup>

The difference between the severity of infectious hepatitis in children and in adults is comparable to the difference which exists between the childhood and adult forms of the more common virus infections. Measles, mumps, and chicken pox are all likely to be more severe and attended by more severe complications in the adult than in the child.

#### SUMMARY

Two institutional outbreaks of infectious hepatitis among children were studied. In all of the ninety-six juvenile patients the disease was mild and of relatively short duration as compared with statistics on the adult disease.

The mildness of infectious hepatitis in children has tended to belittle the disease. There is no evidence that such mild cases are less dangerous to the community from the infectious standpoint than are the more severe adult cases.

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## HYPERCALCEMIA AND IDIOPATHIC HYPERPLASIA OF THE PARATHYROID GLANDS IN AN INFANT

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THE presence of extreme hypercalcemia in a patient who had hyperplasia of the chief cells of all four parathyroid glands is difficult to reconcile with the prevailing views on the abnormalities of serum calcium concentration in relation to the pathology of the parathyroid glands.<sup>1</sup> Chief cell hyperplasia has been associated with secondary hyperparathyroidism, and although instances of hypercalcemia have been reported as resulting from secondary hyperparathyroidism, it is difficult to conceive of such a disturbance on present theoretical grounds. Indeed, as pointed out by Albright,<sup>2</sup> the cases used to exemplify this contention were incompletely studied. Primary hyperparathyroidism associated with enlargement of all four parathyroid glands has been generally conceded to have distinctive histologic alterations in glands. Large cells of the water-clear type alone comprise the parathyroids in all the accepted cases reported to date.<sup>1, 3</sup>

Explanation of the underlying disturbance in this case of a 10-month-old infant with extreme hypercalcemia and enlargement of all four parathyroid glands might contribute much to the knowledge of disorders of calcium and phosphorus metabolism. It is hoped that the description of this patient will lead to the discovery of similar patients and subsequent clarification of the nature of the disorder.

### CASE REPORT

The patient was a white male infant who was studied in the Infants' Hospital from the fifteenth to the twenty-fifth weeks of life and again from the thirty-seventh to the forty-third weeks. Hypercalcemia was revealed during the first admission and most of the subsequent investigations were designed to discover the cause of this abnormality.

The patient's family history disclosed no relevant disturbances. One 7-year-old sibling was said to be healthy. The pregnancy and delivery were normal. The birth weight was 7 pounds and was not regained until the thirteenth day, although both breast and complemental feedings were given during this period. The only disturbance during the neonatal period was icterus without anemia during the first week. From the second to the fifteenth weeks of life an adequate milk modification formula supplemented by 5 drops of oleum percomorphum was offered. Thereafter a variety of modified formulas were tried and solid foods were introduced at five months, although they were always taken poorly. A diet low in calcium (160 to 210 mg. per day) was given during the last week of life. The supplements of vitamin D are recorded in Table I.

From the first few weeks of life until the forty-second week, the patient's symptoms, both from the history and observations in the hospital, consisted of weakness, hypotonia, lethargy, poor appetite resulting in the refusal of much of the food offered, persistent constipation, and occasional episodes of forceful vomiting. Isolated rises of temperature up

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TABLE I. VITAMIN D INTAKE

AGE (WEEKS)	VITAMIN D (U.S.P. UNITS PER DAY)
3-5	720
6-14	900
15-17	1,500
18-20	1,000
21-22	3,000
23-24	0
25-37	800
38-	0

to 102° F. were recorded approximately once a week during both periods of hospitalization, although persistent fever was uncommon. Apparent tenderness of the extremities was noted when the patient was 8 months old.

Physical examinations consistently revealed a small, poorly nourished, weak, irritable child appearing chronically ill and apparently retarded in physical activity and mental capacity. In addition, a firm, smooth liver edge was palpable 2 cm. below the costal margin, and firm masses were felt in the region of each kidney. These latter masses were interpreted as representing slight enlargement of each kidney. Body measurements were consistently below the ten percentiles for normal individuals in the same age group. The patient weighed 8 pounds 7 ounces at 15 weeks of age; 10 pounds 2 ounces at 25 weeks and 11 pounds 8 ounces at 41 weeks. The course of the patient was essentially unchanged until the final week of life. The treatment during the two hospital admissions is outlined as follows:

During the first hospital admission, the patient received elixir of ferrous sulphate for nine weeks; sulfadiazine plus potassium citrate for eight weeks; penicillin, 40,000 units per day, during the fourth to sixth weeks in the hospital; two transfusions of citrated whole blood during the fifth week; and daily intramuscular injections of crude liver extract or vitamin B complex during the last six weeks.

During the second hospital admission, the patient received 40,000 units of penicillin daily until five days before death. A transfusion of citrated whole blood was given three weeks after admission, and elixir of ferrous sulphate was begun at that time. One gram of sodium bicarbonate was given daily during the last sixteen days of life. A specimen of the tibia was taken for biopsy during the second admission.

In the last week of life the patient began to vomit frequently. Two days before death the temperature suddenly rose to 104° F. Physical examination at that time revealed a seriously ill infant with mild cyanosis, labored respirations accompanied by retractions of the supraclavicular and subcostal soft parts, and dullness over the left lung. Coarse rhonchi were present throughout both lung fields. The extremities were cold and mottled. Fluoroscopic examination of the chest showed increased bronchovascular markings bilaterally and slightly increased density throughout the left upper lobe. Treatment with penicillin, oxygen, and fluids did not lower the patient's temperature, although there was slight clinical improvement. During the second day of this episode the patient died, apparently of respiratory failure.

*Laboratory Measurements.*—Table II summarizes the measurements of serum calcium, phosphorus, phosphatase, sodium, chloride, proteins, nonprotein nitrogen, and pH.

The red blood cell counts ranged from 3 to 4 million per cubic millimeter. The white blood cell counts ranged from 8,000 to 16,000 averaging about 12,000 per cubic millimeter.

Repeated examinations of the urine revealed irregular fluctuations in albumin from 0 to 1+, occasional green reduction of qualitative Benedict's solution, and normal urinary sediments. During the interval from 22 to 41 weeks of age, the urine was tested ten times with Sulkowitch's reagent. Little or no calcium was visibly precipitated seven times, although there were, interspersed among these negative reactions, three 2+ reactions. Several measurements of the amounts of calcium and phosphorus excreted in the urine per twenty-four hours are recorded in Table III.

TABLE II. SERUM MEASUREMENTS

AGE (WEEKS)	SERUM CALCIUM (MG. %)	SERUM PHOS- PHORUS (MG. %)	SERUM PHOS- PHATASE (BODAN- SKY UNITS)	SERUM PROTEIN (GM. %)	SERUM SODIUM MEQ. PER L.	SERUM CHLORIDE MEQ. PER L.	SERUM HCO <sub>3</sub> MEQ. PER L.	SERUM PH	NON- PROTEIN NITRO- GEN (MG. %)
21	19.	3.7	12.9	6.0			20.4	7.40	38.4
22	16.9			6.91	137	125			
24	14.8	4.35	12.5	5.8	133	114	18.9	7.30	
27	12.6	2.95	11.0	6.1		111			
37	14.9	3.3	10.3	6.7		106	18.5		30.5
40	19.5			A = 4.69 G = 2.47	137	106	23.		
41						101	22.	7.46	29.5
42	22.1			A = 5.27					
43*	17.3	7.8	8.5	G = 2.28		136			93.

A = Albumin.

G = Globulin.

\*Blood taken just prior to death.

TABLE III. MEASUREMENTS ON TWENTY-FOUR HOUR SPECIMENS OF URINE

VOLUME* (C.C.)	SPECIFIC GRAVITY	PH	CAL- CIUM* (MG.)	PHOS- PHORUS* (MG.)	TOTAL NITRO- GEN* (MG.)	PROTEIN* (GM.)	AMMO- NIA* (MG. N)	AGE (WEEKS)
439			16.4	384	3117	0		23
302	1.023	5.8	20.	310	2416			38
266	1.023	5.4	8.5	304	2394		115	38
290	1.016	6.0	31.4	226			106	42

\*Amounts per twenty-four hours.

The concentration of trypsin in the duodenal contents was normal.

The total serum bilirubin was 0.1 mg. per hundred cubic centimeters. The subcutaneous injection of 0.13 c.c. of 1:1,000 solution of epinephrine hydrochloride provoked a slow rise in the nonfasting blood sugar level from 103 to 123 mg. per hundred cubic centimeters in sixty minutes. A measurement of the urea clearance was performed shortly after the patient was admitted for the second time. The blood cleared of urea per minute was 39.5 c.c., which is approximately 53 per cent of the normal value. During the forty-second week of life, simultaneous measurements of the concentration of calcium in the serum and cerebrospinal fluid revealed values of 22.1 and 8.0 mg. per hundred cubic centimeters respectively. The serum potassium measured in the last sample of blood drawn was 5.8 milliequivalents per liter. A single, three-day metabolic period to determine the balances of calcium, phosphorus, and nitrogen was accomplished during the twenty-fourth week of life. The results are depicted in Table IV. Due to the severe degree of constipation it cannot be assumed that the stools ascribed to this period represented the total fecal output derived from the measured intake.

TABLE IV. THREE-DAY BALANCE PERIOD\* (AGE, 23 WEEKS)

	CALCIUM (MG.)	PHOSPHORUS (MG.)	NITROGEN (GM.)
Intake	1,025	758	4.33
Urine	16	384	3.12
Stool	806	184	0.37
Balance	+203	+190	+0.84

\*Amounts per twenty-four hours.

During the thirty-eighth week of life an electroencephalogram revealed a normal tracing, consisting principally of 4 to 6 waves of normal amplitude per second. At about the same time an electrocardiogram was taken. There was sinoauricular tachycardia with a rate of 140 per minute. The P-R interval was 0.14 second and the Q-T interval was 0.23 second, which is shorter than the average of 0.26 second.<sup>4</sup> The electrical axis deviated slightly to the right. There was a one millimeter elevation of the S-T segment in Lead I.

*Roentgenographic Examination.*—Multiple roentgen examinations of the chest, long bones and skull were made during the patient's admissions to the hospital. On serial examination the changes were found to be essentially similar to those seen on the initial films.

Examination of the chest revealed no definite abnormality of the heart; the lungs showed considerable irregularity of aeration with peripheral emphysema and multiple small and poorly visualized areas of focal atelectasis. Throughout each lung the interstitial markings were increased in prominence and there were a few scattered areas suggestive of peribronchial inflammatory reaction. The changes were interpreted as being consistent with a diffuse interstitial pneumonitis with emphysema and lobular atelectasis.

The bones of the thorax, the skull, and the long bones were slightly undercalcified. The trabeculae of the spongiosa seemed diminished in number but increased in prominence. The cortex, particularly of the long bones, showed slight irregularity with some loss of cortical substances at the diaphyseal extremities. The zones of provisional calcification appeared well preserved and there was no definite evidence of uncalcified osteoid tissue to suggest rickets.

Roentgen examination of the abdomen and intravenous urograms showed slight enlargement of the liver and each kidney. Diodrast appeared promptly in each renal pelvis in five minutes and was transported normally to the bladder. There was no evidence of obstructive uropathy or other abnormality except for the slight enlargement of the kidneys. Calcification of the soft tissues could not be detected.

*Biopsy.*—A biopsy of the tibia, taken seventeen days before death, revealed fibrosis of the marrow spaces, a disturbance of bone growth, and hyperplasia of the remaining hematopoietic elements. On the basis of these findings, a diagnosis of hyperparathyroidism was suggested.

#### AUTOPSY

Postmortem examination was performed four hours after death and was limited to examination of the abdominal and thoracic contents. The body was that of a poorly developed and poorly nourished infant, measuring 63 cm. in length (normal length, 69 cm.).<sup>5</sup> Examination of the external surface of the body revealed a 4 cm. healed, vertical incision on the anterior surface of the middle third of the tibia.

The weights and measurements of the viscera, with normal weights in parentheses,<sup>5</sup> were: heart, 36 Gm. (39 Gm.); lungs, 80 Gm. (105 Gm.); spleen,  $5.6 \times 3.5 \times 1.2$  cm., 13 Gm. (22 Gm.); thymus,  $4.7 \times 4.7 \times 1.3$  cm., 8 Gm. (20 Gm.); liver,  $16.5 \times 8.2 \times 4.5$  cm., 218 Gm. (274 Gm.); right kidney,  $6.7 \times 3.8 \times 2.3$  cm., 40 Gm. (32 Gm.); left kidney,  $7.2 \times 3.5 \times 2.5$  cm., 38 Gm. (31 Gm.); right adrenal,  $3.7 \times 2.3 \times 0.5$  cm., 2 Gm.; left adrenal,  $3.9 \times 1.7 \times 0.3$  cm., 2 Gm.; testes, 1 Gm. each; and parathyroids,  $0.8 \times 0.2 \times 0.2$  cm.,  $0.5 \times 0.2 \times 0.1$  cm.,  $1.0 \times 0.4 \times 0.2$  cm., and  $0.6 \times 0.3 \times 0.2$  cm.

The pericardial, pleural, and peritoneal cavities were lined by smooth, moist, and glistening membranes. Two cubic centimeters of clear fluid were present in the pericardial sac, but no free fluid was found in the pleural or peritoneal cavities.

Gross and microscopic examination of the heart, alimentary tract, liver, pancreas, adrenals, testes, diaphragm, thymus, and salivary glands was essentially normal, except for generalized congestion and edema of moderate degree. The liver showed marked edema.

The lungs were the site of a generalized interstitial pneumonia. The pleural surfaces were smooth, dark reddish-purple posteriorly, and pale pink anteriorly. There was crepitation anteriorly, but a firm consistency in the posterior portions of all lobes. Section revealed flat, pinkish-red, dry surfaces. The trachea and bronchi contained a white, thick, mucoid



Fig 1



Fig. 2.

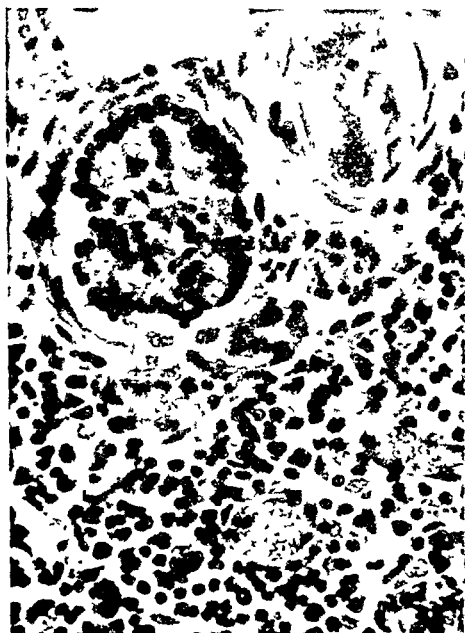
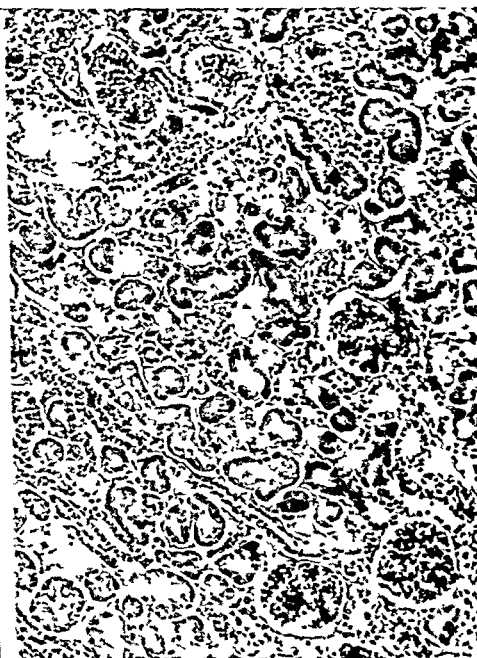


Fig 3



Fig 4

Fig 1—Right kidney and aorta showing radiating deposits of calcium in cortex and medulla. Arrow points to region of small plaques in aorta and iliac arteries.

Fig 2—Medium power view of kidney showing preservation of normal renal architecture of the glomeruli and proximal tubules, especially.

Fig 3—Focus of lymphocytic infiltration in cortex of kidney.

Fig 4—Low power view of kidney (von Kossa stain). Note preservation of general architecture. The dark staining material near the corticomedullary junctions represents calcium casts.

Fig. 5.



Fig. 6.



Fig. 7.



Fig. 8.

Figs. 5 and 6.—Low power views of kidney showing calcium casts and increased interstitial fibrosis.

Fig. 7.—Arrows point to parathyroids.

Fig. 8.—Arrows point to additional structures removed, two of which proved to be parathyroids.

Fig. 9.

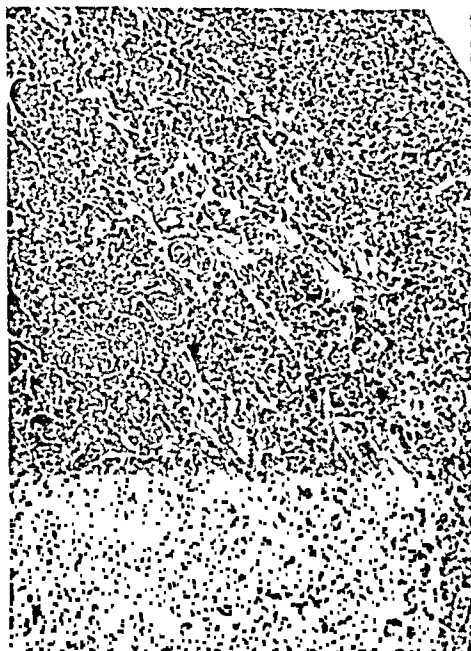


Fig. 10.

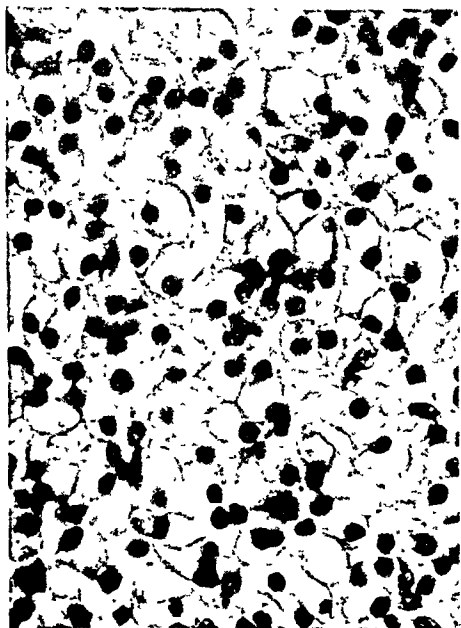
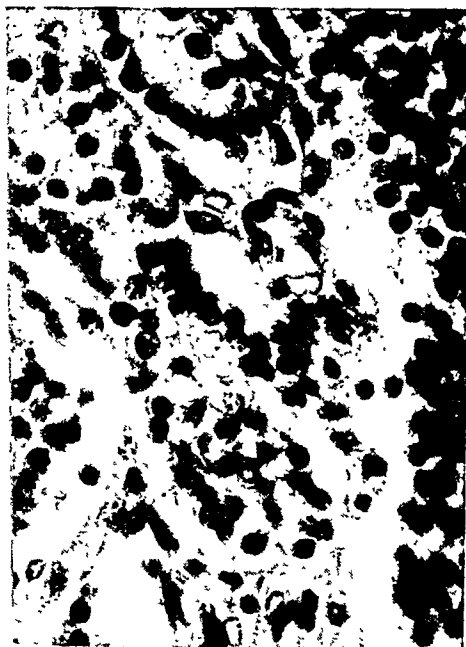


Fig. 11.

Fig. 12.

Fig. 9.—Low power view of parathyroid showing dense cellularity.

Fig. 10.—High power view of normal parathyroid gland of patient aged 10 months, dying of hydrocephalus with complicating infections. Note the amount of stroma and looseness of cellular arrangement.

Fig. 11.—High power view of parathyroid showing the large number of chief and transitional water-clear cells and the compactness of the cellular arrangement.

Fig. 12.—View of aortic wall showing medial calcification.

Fig. 13.



Fig. 14.

Fig. 13.—High power view of rib showing osteoclasts adjacent to cortical bone in shaft of rib

Fig. 14.—Rib showing fibrosis of marrow spaces and increased numbers of osteoclasts.

material. The hilar lymph nodes were firm, pale red, and discrete. Microscopic examination showed generalized thickening of the alveolar walls, due to infiltration of large mononuclear cells and congestion of the capillaries. There were foci of emphysema and partial atelectasis. Most of the alveoli were empty, but a few contained ringlets of precipitated protein or small numbers of large mononuclear cells. Some of these mononuclear phagocytes contained brown granules of pigment in their cytoplasm. One section included a group of alveoli and a few bronchioles filled with extravasated red blood cells. There was marked edema of the interlobular, subpleural, and perivascular connective tissues. The capillaries and small vessels were markedly congested.

The malpighian corpuscles of the spleen, the mesenteric lymph nodes, and the lymphoid follicles of the large intestine showed the nonspecific changes of a marked toxic reaction with enlargement of the germinal centers and phagocytosis of cellular debris by the reticuloendothelial cells.

The most outstanding pathologic changes were seen in the parathyroids, kidneys, and skeletal system. The kidneys were enlarged. The capsules were thin and transparent. They stripped easily, revealing smooth, pale pinkish-red, external surfaces with shallow remnants of the fetal lobulations. The tubular markings on the surface were prominent as white foci averaging 0.15 cm. in diameter surrounded by thin, red, vascular markings. On sectioning the kidneys, there was a distinct gritty sensation. The cut surfaces bulged slightly and the corticomedullary junctions and tips of the pyramids were congested. Fine, white chalky lines radiated through the pyramids, medulla, and cortex, being especially numerous near the corticomedullary junction (Fig. 1). The calyces, pelves and ureters were patent and lined by a smooth, pinkish-gray, intact mucosa.

On microscopic examination, the general pattern of the renal architecture was preserved (Fig. 2). Most of the glomeruli appeared normal, but a very small number in each kidney showed one or more of the following changes: slight increased cellularity of the tufts; thickening of the layers of Bowman's capsule with crescent formation; and granular eosinophilic precipitate with occasional large mononuclear cells in the subcapsular spaces. Scattered through the interstitial tissues were small foci of infiltrated lymphocytes, plasma cells, and neutrophils (Fig. 3).

The proximal convoluted tubules contained small amounts of granular, eosinophilic debris, except for a few which were greatly dilated with granular, grayish-blue casts. The loops of Henle contained small numbers of bluish casts that stained black in a von Kossa preparation (Fig. 4). Many of the collecting tubules contained similar large calcium casts. Some of the calcium was deposited around the tubules in the interstitial tissues, and a few calcium masses were seen in the walls of small arterioles in the cortex. The medulla and pyramids contained the greater part of the calcium. There was moderate to advanced increase in the interstitial fibrous tissue of the medullary regions (Figs. 5 and 6).

The parathyroid glands were grossly identified as small, pinkish, firm nodules along the lateral and posterior aspects of the thyroid gland (Figs. 7 and 8). On microscopic examination, all four glands were more cellular than normal and no stromal fat separated the cellular strands (Figs. 9 and 11). The predominant cell types were the chief cells and transitional water-clear cells\* (Fig. 11).<sup>\*</sup> A few small foci consisted of the large, water-clear cells. In scattered areas some of the cells showed nuclei arranged near the pole of the cell next to the stroma. Early attempts at pseudoacinar formation were seen. One cyst was noted containing granular, eosinophilic material and lined by chief cells. No oxyphilic cells were identified.

The only evidence of metastatic calcification was the presence of several small plaques of calcium deposited in the media of the abdominal aorta and iliac arteries (Figs. 1 and 12).

\*Because of the conflicting terminology used in textbooks and articles concerning the histology of the parathyroid glands this note is added. Chief cell in this paper refers to the small cell with stainable cytoplasm that comprises the major portion of the gland. Transitional water-clear cell refers to a cell of the same size as, or slightly larger than, a chief cell, with a similar nucleus, but with clear and unstaining cytoplasm. Large water-clear cell refers to a cell that is much larger than the chief cell, has a similar nucleus, and no stainable cytoplasm. Oxyphile cell designates a cell with eosinophilic, cytoplasmic granules.

Microscopic preparations of the ribs revealed replacement of the hematopoietic tissue in the marrow spaces by collagenous tissue in which large numbers of osteoclasts and osteoblasts were identified (Figs. 13 and 14). The peripheral spaces were more densely replaced by fibrous tissue than the central marrow spaces, and in many places this fibrous tissue was continuous with the periosteum. Scattered foci of hematopoietic tissue were identified near the costochondral junctions, but became larger, hyperplastic, and more numerous farther from the junction. The lines of ossification were slightly irregular, with several columns of undegenerated cartilage cells extending beyond the zone of provisional calcification. Capillary penetration was fair.

An incidental finding was the presence of double ostia to the right coronary artery. No other congenital anomalies were noted.

#### COMMENTS

The outstanding abnormalities appeared to be an elevation of the serum concentrations of calcium and chloride, a decreased urea clearance, a low urinary excretion of calcium, diminished serum bicarbonate, hyperplasia of all four parathyroid glands due to increased numbers of chief and transitional water-clear cells (see previous footnote), *nephrocalcinosis*, and *osteitis fibrosa*.

The ionized calcium was increased as evidenced by the characteristic clinical symptoms, by the level of the spinal fluid calcium, and by calculation from the data in Table II. Since the serum inorganic phosphorus was usually below 4 mg. per hundred cubic centimeters, it should be regarded as abnormally low for the age of the patient.<sup>7</sup> The terminal episode which seemed to be an acute pneumonic infection, closely resembled the clinical and laboratory observations recorded from patients suffering from excessive amounts of parathyroid hormone.<sup>2, 8</sup> Only a single, short, metabolic balance period could be accomplished. In this period, when the intake was above that generally maintained by the patient and while vitamin D was omitted from the diet, the significant features were: the positive balances of calcium, phosphorus, and nitrogen, the relatively high ratio of calcium to phosphorus in the stools, and the small quantity of calcium in the urine. The photomicrographs show the predominantly chief and transitional water-clear cell structure of the parathyroid glands; the presence of calcium casts in the renal tubules with moderately increased interstitial fibrosis of the medulla and with preservation of most of the general renal architecture; and the replacement fibrosis of the marrow spaces with increased osteoblastic and osteoclastic activity.

#### DISCUSSION

The material presented poses several questions of importance to those interested in calcium and phosphorus metabolism. Did this disorder represent an instance of primary hyperparathyroidism in which the structure of the parathyroid glands differed from that previously accepted? If so, are these changes representative of primary hyperparathyroidism during infancy? Or was the fundamental disturbance one of secondary hyperparathyroidism which ceased to perform its service as a compensatory reaction and progressed to unbridled production of parathyroid hormone?

An attempt to clarify certain aspects of our observations will be made in the following paragraphs without the expectation that definite answers to the preceding questions can be reached from this study alone.

Excessive intake of vitamin D as a cause of this disorder seems to be excluded by the patient's course in relation to the intake of this vitamin.

Chown<sup>9</sup> reported two infants with hypercalcemia, nephrocalcinosis, and disturbances of the bones, and he postulated a primary diencephalopituitary lesion as the cause of the symptom complex. Although the brain and pituitary gland of our patient were not available for examination, the roentgenographic appearance and histologic structure of the bones in Chown's cases did not resemble our findings. Furthermore, Chown found no abnormality of the parathyroid glands in his patients.

The combination of impairment of renal function and enlargement of the parathyroids occurs most often as the result of primary renal disease. Chronic acidosis might lead to hypercalcemia because of the withdrawal of calcium from the bones, and both renal calcification and osteitis fibrosa have been associated with chronic acidosis.<sup>10, 11</sup> Nevertheless, we feel that renal damage was not the basic factor in this instance because of the practically stationary roentgenographic appearance of the bones, the failure of the hypercalcemia to be reduced when the acidosis was corrected by the administration of sodium bicarbonate, and the preservation of renal tissue on histologic examination. The ability of the kidneys to concentrate the glomerular filtrate, to produce ammonia, to alter the pH of the urine, and to maintain a normal value of nonprotein nitrogen and a low inorganic phosphate in the serum, all seem to oppose the hypothesis of primary renal damage.

The possibility that the basic disturbance was primary hyperparathyroidism is supported by the constancy and duration of the clinical symptoms, the progressive hypercalcemia, the frequently low serum inorganic phosphate, and the fact that the clinical picture seemed to fit no other disease.<sup>12</sup> Atypical features were the low urinary calcium output, the positive calcium and phosphorus balance, and the morphology of the parathyroid glands. Undisputed examples of primary hyperparathyroidism with low urinary calcium excretion have been reported. Secondary renal damage is said to account for the unexpectedly small output of calcium in the urine in such cases. In the present patient, the resorption of large amounts of calcium from the glomerular filtrate must have occurred in spite of the high level of serum calcium, because calculations utilizing the estimated diffusible calcium concentration in the serum and the urea clearance indicate that many times the amount of calcium found in the urine should have been present in the glomerular filtrate. The single determination of positive calcium and phosphorus balances might be explained either as a result of the high intake of these minerals in the usual diet for infants, or as representing a transient situation occurring during a period of slight clinical improvement. Similar studies while on a low calcium diet would be expected to reveal more pertinent information. These were contemplated, but could not be completed.

Effective treatment necessitates a more complete understanding of the physiologic disturbances than is available. Until more evidence is obtained, it would seem that prompt recognition of this condition, competent description of the disturbed physiology by means of carefully planned and rapidly executed studies, and then removal of a portion of the hyperactive parathyroid tissue would provide the greatest opportunity for survival, as well as for the acquisition of knowledge concerning the underlying process. The relatively rapid deterioration of the physical condition of our patient emphasizes the need for prompt recognition and study of such patients lest the opportunity for successful treatment be lost.

#### SUMMARY AND CONCLUSIONS

The clinical and laboratory investigations of a 10-month-old infant exhibiting extreme hypercalcemia, mild acidosis, impairment of renal function, and low urinary excretion of calcium have been presented. The post-mortem examination revealed chief cell hyperplasia of all four parathyroid glands, nephrocalcinosis, and osteitis fibrosa.

The apparently unique combination of hypercalcemia and chief cell hyperplasia of the parathyroids was not satisfactorily explained from our observations.

It is hoped some of the issues raised by this study will be solved by the investigation of similar patients.

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# BONE MARROW INFUSION IN CHILDHOOD

## EXPERIENCES FROM A THOUSAND INFUSIONS

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THE employment of bone marrow infusion was adopted almost simultaneously by various pediatric clinics in Denmark in the spring of 1943. We now have three to four years' experience in the employment of the method, and at the time of writing, in the summer of 1946, we have available data on close to 1,000 infusions given to 495 patients, the largest amount of information of this kind hitherto reported.

On the basis of this material we shall deal with several problems which, we think, have not been sufficiently discussed in the literature, and which have led to some misunderstandings, particularly in regard to the questions of technique and the risk of osteomyelitis.

The historical development of the bone marrow infusion has been mentioned in several papers. The suitability of the bone marrow for infusion was demonstrated as early as 1922 by Drinker and associates<sup>13</sup> and Doan.<sup>12</sup> At the Scandinavian Congress in Uppsala in 1933, Josefson<sup>20</sup> reported that in ten cases of pernicious anemia he had injected Campolon directly into the sternal marrow, and thought that he had obtained a good depot effect. In 1937, Benda and collaborators<sup>7, 8</sup> reported injections of bacteria as well as drugs and contrast media into the bone marrow. In 1940, Henning<sup>18</sup> published his paper on intra-sternal transfusion; and in 1940-41, Tocantins<sup>35</sup> and Tocantins and O'Neill<sup>36</sup> reported their classical studies on bone marrow infusion.

In Denmark, blood transfusion via the bone marrow was first employed by Bang and associates<sup>5</sup> in 1942.

Through the following years, especially in the English literature, a number of reports have been published, in which practically all the authors who have employed the method to a fairly large extent recommend it and describe it as a great advantage in pediatrics.<sup>1-4, 6, 9, 11, 14-17, 24, 27, 29, 32, 37-40</sup> It is asserted more or less indiscriminately that substances suitable for intravenous injection could also be injected via the bone marrow. We wish to emphasize at once that we do not subscribe to this view, for reasons that will be given later. Even in their first paper, Tocantins and O'Neill<sup>36</sup> warned against the employment of hypertonic or other irritant solutions, a warning to which Wallden<sup>41</sup> recently has subscribed. The osteomyelitis literature will be reviewed in a subsequent section.

### TECHNIQUE

The technique employed in the thousand infusions here discussed was developed by Kjøster.<sup>21, 22</sup> In our opinion, it represents the safest and, certainly, the simplest procedure described so far. In practically every case the infusion

From the University Clinic of Pediatrics and the Surgical Clinic C, the Rigshospital, and from the Queen Louise's Children's Hospital, Copenhagen.

is given in the ward with the child lying in his bed. The leg is fixed manually by a nurse; the surgeon merely washes his hands well, not as prior to an operation, and he wears no gloves or mask, as has been insisted upon by some authors.<sup>1, 15, 24</sup> Briefly, the procedure is as follows:

After the usual blood grouping and direct compatability test, the blood from the donor is withdrawn into a low, wide graduate (7 to 8 cm. in diameter). We have found the graduate of this size most practical, and we have used the addition of 1 part 3.80 per cent sodium citrate to 9 parts blood. After ordinary, thorough disinfection of the skin with iodine, the skin over the upper half of the tibia is tightened between two fingers, and the special bone-puncture cannula (Køster model, Fig. 1) is introduced by a light, boring motion in the middle of the anterior aspect of the tibia, about 3 cm. below the joint line, directed a little distally. One is never in doubt as to when the cortex is perforated. In only

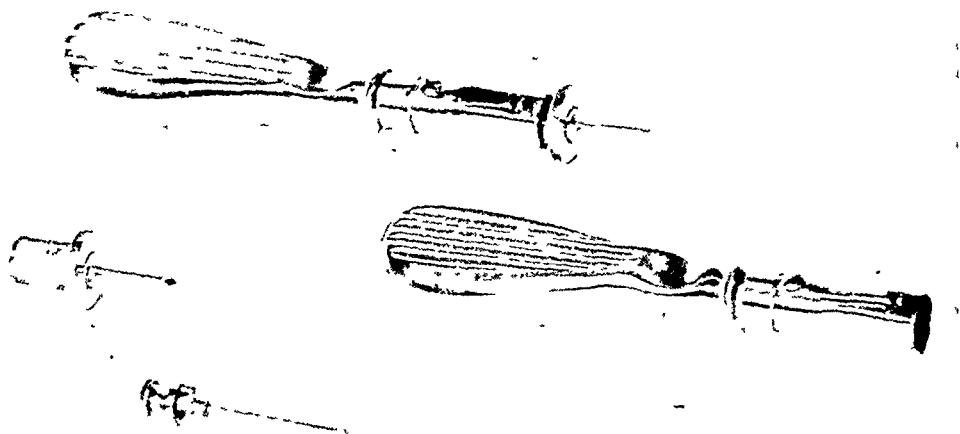


Fig. 1.—Køster model special bone-puncture cannula.

a few cases was local anesthesia applied beforehand (extending beneath the periosteum), as it is our impression that for children under 2 years this measure is quite superfluous and it made no difference in their reaction. On the other hand, in some cases of children over 2 years we have performed the puncture under slight ether anesthesia. After the introduction of the cannula, we make sure that it is situated in the free marrow space by means of aspiration with a 10 c.c. syringe, half filled with saline. This is of fundamental importance. (At this juncture some marrow may be aspirated for examination just as in ordinary sternal puncture.) After removing the syringe, a little blood and marrow will trickle out of the cannula if this is situated properly, showing that the cannula is free from air.

The transfusion is performed most conveniently by means of two 10 c.c. Record syringes, one being filled by an assistant while the blood in the other is being infused. The operator should, of course, make sure that the syringes contain no air.

Usually the infusion meets slight resistance, and this often subsides somewhat after infusion of the first 20 to 30 c.c. If, at this juncture, one feels more than a very slight, springy resistance, the cannula is not situated properly (it may, for instance, have entered one of the sides of the tibia), and its placing has to be corrected, preferably by introduction into the other tibia or into the distal part of the shaft of the femur. The same applies if oozing appears at the site of insertion, sometimes commencing with swelling of the subcutaneous tissue of the leg.

The maximal rate of infusion employed by us has been 10 c.c. per minute. And, as a rule, the infusion dose has been about 20 c.c. blood per kilogram of body weight.

#### CLINICAL MATERIAL

The present material is gathered from the following seven pediatric clinics in Copenhagen: The Blegdam Hospital (Epidemic), the Fuglebakken Children's Hospital, the Queen Louise's Children's Hospital, the Municipal Pediatric Clinic on Martinsvej, the Northern Hospital, the Pediatric Clinic of the Rigshospital, and the Pediatric Clinic of the Sundby Hospital.

The material comprises 495 patients who received a total of 982 bone marrow infusions in the period from the spring of 1943 to the spring of 1946, eighteen unsuccessfully.

The indications for the infusions will be evident from Table I, which gives the various diagnoses made.

TABLE I. DIAGNOSES OF PATIENTS WHO RECEIVED BONE MARROW INFUSIONS

DIAGNOSIS	NUMBER	DEATHS
Acute gastroenteritis with intoxication	338	127
Chronic dyspepsia	32	2
Fetal erythroblastosis	19	5
Pneumonia with complications	16	6
Meningitis	10	5
Anemia	8	1
Sepsis	8	6
Premature birth (congenital debility)	8	5
Leucemia	6	4
Tetanus neonatorum	5	3
Blood dyscrasias with hemorrhage	5	2
Hemorrhagic disease of the newborn	5	0
Various abscesses	4	3
Peritonitis	4	3
Congenital pyloric stenosis	4	0
Hemolytic anemia	3	0
Agranulocytosis	1	0
Various other diseases	19	7
Total	982	179

The group "various other diseases" comprises a number of different infectious diseases. As our material includes but a few patients with primary surgical illness, one of the most important indications, acute traumatic shock, is not represented here.

Many patients were given bone marrow infusion more than once, one patient as often as 10 times. Only in exceptional cases did the infusion fluid ooze out through the previous punctures. Continuous infusion was given to five

patients for up to thirty-two hours. Of these patients, four died under the infusion. The survivor contracted osteomyelitis (see below). The distribution of the total number of infusions follows:

<i>Number Patients</i>	<i>Number Infusions*</i>
231	1
142	2
61	3
31	4
16	5
7	6
2	7
4	8
1	10

As a rule, infusions were not given at intervals shorter than two days, but they may very well be given at shorter intervals if necessary. Thus, in this series of cases, there were some patients who received five infusions within three days, and three of these infusions were given within twenty-four hours.

The youngest patient was 2 days old, the oldest, 4 years. The smallest patient weighed 1,200 Gm. In these extreme cases, the performance of the infusion met with no difficulty whatever.

The infusion fluids employed are listed in Table II.

As will be noticed from Table II, in several cases various remedies were given via the bone marrow. Particular mention is to be made of the injection of 50 per cent glucose, which was given to twenty-three patients in thirty-two infusions, as a rule in doses of 10 c.c.

TABLE II. INFUSION FLUIDS EMPLOYED

INFUSION FLUID	NUMBER INFUSIONS
Blood	696
Serum	174
Sodium bicarbonate	78
50 per cent glucose	22
Antitetanus serum	6
Perabrodil	3
30 per cent sodium sulfate	2
Calcium gluconate	1
Total	982

This form of treatment is not free from risk, as three of these patients (13 per cent) acquired osteomyelitis. The series includes two additional patients with osteomyelitis. These five cases will also be discussed later.

The infusion of serum has given rise to complications. The serum employed has been chiefly dry human serum, prepared by the State Serum Institute, Copenhagen. Beside the usual elements, the serum contains 5 per cent glucose. Specific antipneumococcus serum was employed in a few cases, and also scarlatinal convalescent serum.

Two patients died within twenty-four hours after intratibial administration of dry serum. The case histories of these two patients are as follows:

\*Five of these patients were given continuous infusion.

CASE 1.—This patient was a 1-month-old boy, admitted for acute gastroenteritis with intoxication. As his condition remained poor, seventeen days after admission he was given 70 c.c. dry serum intratibially, without inconvenience. Twelve days later (twenty-nine days after admission), he had pronounced edema, for which he again was given 70 c.c. dry serum (29 c.c. per kilogram) intratibially, given in the course of fifteen minutes. About one hour later, he suddenly became exceedingly ill, shocked, pale, and cyanotic, with shallow respiration. In spite of stimulants, he died within one hour.

Autopsy diagnosis: perivascular cerebral hemorrhage, slight degree; diffuse pulmonary hemorrhages, recent and older; aspiration of meconium, slight degree; congestion of the spleen, slight degree.

CASE 2.—The patient was a boy, 16 days old, admitted for acute gastroenteritis with intoxication. On account of pronounced debility, on the day after admission the patient was given intratibial blood transfusion without inconvenience. One week later, moderate edema appeared. The patient was given dry serum intratibially (of the same lot of serum as given in Case 1), 35.7 c.c. per kilogram, without any immediate inconvenience. Ten hours later, the patient suddenly became listless, whining a little, with Cheyne-Stokes respiration and imperceptible pulse. At first he responded to stimulants, but an hour later he again became desperately ill and died in spite of stimulation.

Autopsy diagnosis: acute gastroenteritis; capillary bronchitis to a marked degree; bilateral atelectasis to a marked degree; congestion of the abdominal viscera.

In three additional cases the patients collapsed after serum infusion which had given no difficulty whatever, two of the patients about one hour after the infusion, the third about ten hours afterward. However, these children responded well to the stimulants given.

In eighteen cases the bone marrow infusion had to be recorded as a complete failure (1.8 per cent) as repeated attempts to enter a free marrow cavity failed in both tibias, or infusion of the fluid soon became blocked, after which the infusion was given up. Trouble of this kind may be due to the circumstance that the venous sinuses of the marrow, which afford the connection with the veins of the cortex (Meurling,<sup>23</sup>) have not developed sufficiently. On the other hand, it should be mentioned that it was possible to give an infusion to several patients a few days later without any difficulty whatsoever.

In spite of the relatively simple technique involved, the avoidance of such difficulties appears to be largely a matter of experience. Thus, it was found that in one hospital where 436 of the 1,000 infusions had been given, difficulties of this character were encountered in only twenty-six patients (in 6 per cent as against 9.9 per cent for the rest of the cases).

In 8.2 per cent of the patients the infusion did not proceed smoothly but it was still carried through, mostly by changing from one tibia to the other. The troubles most often encountered have been difficulties in entering a free marrow cavity. In other cases a considerable hematoma has formed at the site of the injection, causing swelling of the entire extremity in one patient. In some cases a hematoma has formed on the posterior aspect of the leg, signifying that the cannula has been forced straight through the tibia. Finally, mention is to be made of occasional technical difficulties such as bending of the needle, and sticking of the piston in the syringe.

None of the last-mentioned minor difficulties gave any lasting inconvenience.

Thus it is to be pointed out that 686 intratibial blood transfusions were given with this technique, without any serious complication whatsoever, whereas injection of hypertonic fluid and permanent infusion have given serious complications.

#### HISTOLOGIC EXAMINATION

Even though injection of contrast media has shown that, as far as absorption is concerned, intraosseous injection fully comes up to the level of intravenous injection, the idea still suggests itself that the bone marrow infusion might bring about some injury to the proximal tibial epiphysis. This is not the case, however. In eleven patients who died within fourteen days after the infusion, the respective tibiae were removed for examination. The only macroscopic finding was the site of the insertion of the needle, about as thick as a pin. In no specimen was any abnormal feature seen to arise from this site. In every specimen the epiphyseal line was found to be perfectly normal microscopically.

#### ROENTGENOLOGIC EXAMINATION

Even though the histologic examination revealed nothing suggestive of any injury to the epiphyseal line, and even though clinical control with an observation period of over three years for the first treated patients in no instance has disclosed any disturbance of the growth, we still found it to be of great interest to investigate, through systematic roentgenologic control, whether there might be any demonstrable, permanent, roentgenographic changes in the tibia after a considerable length of time. This seemed desirable, as some authors have reported roentgenologic changes in the form of noticeable drilling holes and periosteal reactions in immediate connection with the infusion.<sup>10, 32, 41</sup>

Of our 495 patients, seventy-two were examined roentgenographically as follows:

- I: 36 patients were examined 0 to 1 year after the infusion.
- II: 18 patients were examined 1 to 2 years after the infusion.
- III: 18 patients were examined over 2 years after the infusion.

*Group I.*—A majority of these patients were examined within six months after the transfusion. In the first weeks after the transfusion, several of the examinees showed noticeable sites of puncture, a little over pin-head size, with slight, though unquestionable, marginal sclerosis. In our series this phenomenon was demonstrated in six patients, but it was never observed more than six months after the infusion, and as a rule it seemed to disappear much sooner. Two patients who had been given eight and four intratibial transfusions respectively, presented a slightly irregular structure of the proximal end of both tibiae. Another patient had been given four transfusions within seven weeks, each time with difficulty, as each time it proved necessary to change from one tibia to the other. At one attempt, a hematoma of the right leg appeared. Fig. 2 shows sites of puncture with sclerosis and slight structural changes in the proximal part of the metaphysis of the right tibia. In addition, there are distinct, periosteal deposits that presumably can be interpreted as evidence of a rather considerable subperiosteal hematoma.

Thus it may be looked upon as established that simple blood transfusion via the bone marrow in a certain, relatively small number of patients gives rise to slight roentgenographic changes. The significance that is to be attached to these changes will be evident from Groups II and III.

*Groups II and III.*—These two groups, which represent the real follow-up examination, gave an indisputable result: none of the thirty-six patients, who were picked out quite at random, showed any roentgenologic abnormality, and in every instance the growth of the bone had proceeded normally on both sides. This outcome is the more significant when we consider that the eighteen patients with an observation period of over two years received their transfusion at a time when the experience in the technical procedure was not as great as later on. Furthermore, in one of these patients a considerable subperiosteal hematoma had appeared immediately after the transfusion; and, as mentioned above, in several cases the attempts at transfusion had failed in part.

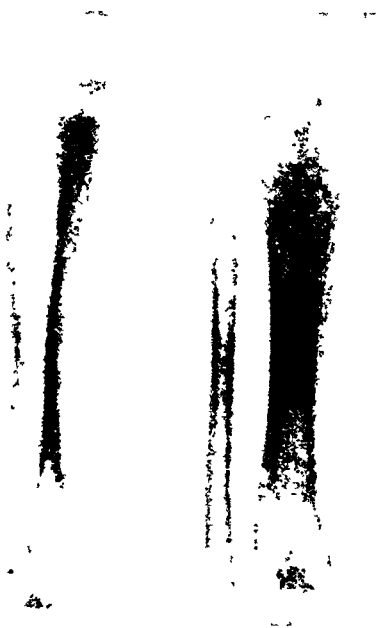


Fig. 2.—Roentgenogram of patient in Group I, showing sites of puncture with sclerosis and slight structural changes in the proximal part of the metaphysis of the right tibia. Distinct periosteal deposits can be interpreted as evidence of subperiosteal hematoma.

The result of the x-ray examination may be summed up to this effect: simple blood transfusion via the tibial bone marrow may sometimes give transitory, but not permanent, roentgenologic changes, and thus should not disturb the growth of the bone.

#### OSTEOMYELITIS

The only serious complication that may arise from bone marrow infusion is osteomyelitis. In the literature accessible to us, only a few instances of the

complication have been mentioned, and we have found no attempt to estimate how serious this complication may be. The patients we have found reported in the literature are listed in Table III.

TABLE III. OSTEOMYELITIS FOLLOWING BONE MARROW INFUSION: PATIENTS REPORTED IN LITERATURE

AUTHORS	NUMBER INFUSIONS	PATIENTS WITH OSTEOMYELITIS
Behr <sup>6</sup>	40	1
Gunz and Dean <sup>15</sup>	35	3
Quilligan and Turkel <sup>29</sup>	45	1
Rooney <sup>33</sup>	100	2
Tocantins, Price, and O'Neill <sup>40</sup>	79	3

Behr's patient had been given continuous intratibial infusion. The osteomyelitis yielded promptly to surgical treatment.

In two of the three cases reported by Gunz and Dean<sup>15</sup> the patients had been given blood transfusions, and on this account the authors feel justified in advising against infusion of whole blood. No mention is made of the clinical course of the three cases; all three patients had been given continuous infusion.

In the case reported by Quilligan and Turkel<sup>29</sup> the patient was given intratibial infusion for four days on account of peritonitis and, possibly, sepsis. Autopsy two days later revealed an extensive inflammatory process comprising practically the entire bone marrow.

The two patients reported by Rooney<sup>33</sup> had osteomyelitis after continuous infusion. In one, the inflammation was localized at the proximal end of the tibia, in the other, at the distal end of the femur. The first patient was admitted for operative treatment; in the other, a subcutaneous abscess was incised. Both recovered and after five months no deformity could be discovered.

Details in the three cases reported by Tocantins, Price, and O'Neill<sup>40</sup> are unknown to us, as we have had no access to the original paper.

Reisman and Tainsky<sup>31</sup> mention a patient who had a subcutaneous abscess at the site of puncture after a blood transfusion via the bone marrow; the abscess perforated spontaneously. X-ray examination three months later showed pronounced periosteal bone formation at the level of the previous abscess formation, but no destruction of bone. In this case the lesion may hardly be recognized as osteomyelitis.

In our material we have seen five instances of osteomyelitis, the records of which will be given briefly:

CASE 1.—A boy, born Sept. 29, 1944, was admitted to Fuglebakken Children's Hospital, Oct. 6, 1944. The diagnosis was premature birth and acute gastroenteritis with intoxication.

Weight at birth was 2,100 Gm. On August 11, the child was extremely exhausted, and continuous intratibial infusion was given on the left side for thirty-two hours (220 c.c. serum plus 50 c.c. saline). Five days later, there were edema of the left leg and discharge of pus from the site of the puncture. X-ray examination on November 23 showed a rarefaction in the proximal metaphysis. After chiseling, the osteomyelitis lesion healed in two months.



Re-examination at the age of 14 months showed shortening of the left leg amounting to 1 cm., and atrophy of the calf amounting to 0.5 cm. in circumference. The left knee was lacking 10 degrees in complete extension, and there was 10 degrees varus position. Roentgenographically, the structure of the tibia was irregular proximally, with absence of the epiphyseal nucleus. The left tibial diaphysis was 0.5 cm. shorter than the right.

CASE 2.—A boy, born April 18, 1945, was admitted to the Pediatric Clinic of the Rigshospital on May 29. The diagnosis was premature birth, edema, and glioma of the retina.

Weight at birth was 1,150 Gm., weight on admission was 1,750 Gm. On the day before admission the patient was given 10 c.c. of a concentrated serum solution (corresponding to about 40 c.c. normal serum) in the right tibia. Four days later the entire right leg was swollen, with discharge of pus from the site of the puncture. X-ray examination on June 25 showed extensive osteomyelitis with large osseous abscesses in the metaphyses and total necrosis of the entire diaphysis, which was enveloped by a vigorous sequestral capsule. Under surgical treatment the osteomyelitis healed in one month. The patient died at the age of five months from an intercurrent infection.

CASE 3.—A boy, born Nov. 25, 1945, was admitted to Queen Louise's Children's Hospital on November 29, 1945. The diagnosis was acute gastroenteritis with intoxication.

Weight at birth was 1,750 Gm. On Feb. 3, 1946, the patient was given an infusion of 10 c.c. 50 per cent glucose into the bone marrow of the left tibia, followed by saline. On the next day the entire leg was swollen, and a few days later there was secretion from the site of puncture. On Feb. 15, 1946, there was increasing swelling and more profuse secretion from the fistula. X-ray examination on March 2 showed progressive osteomyelitis, and, on March 12, extensive destruction of the proximal metaphysis and vigorous periosteal formation of bone round the entire diaphysis. From March 14 to April 15, the patient had oscillating temperature, with no other demonstrable cause. In response to penicillin therapy the fistula closed, and the inflammatory process subsided. On May 1 both legs appeared perfectly normal; there was no clinical evidence of osteomyelitis.

Re-examination on Sept. 12, 1946, showed 1 cm. shortening of the left leg. On x-ray examination the epiphyseal line was shown to be almost effaced, the zone of ossification irregular, and the metaphysis broadened.

CASE 4.—A male child, born Dec. 2, 1944, was admitted to Queen Louise's Children's Hospital on Dec. 14, 1945, with a diagnosis of acute gastroenteritis with intoxication.

Weight at birth was 3,740 Gm., and weight on admission was 2,700 Gm.

On Jan. 16, 1946, the patient was given an infusion of 20 c.c. 50 per cent glucose into the marrow of the left tibia. Seven days later there was swelling of the entire left leg and secretion of thin pus from the site of puncture. X-ray examination on Feb. 4 showed typical osteomyelitis. On March 4 it showed extensive destruction of the entire proximal metaphysis, and strong periosteal reaction, corresponding to the entire diaphysis. April 3, after treatment with penicillin, a defect was seen in the proximal epiphyseal nucleus of the left tibia and a similar defect in the corresponding metaphysis. The epiphyseal line was indistinct and broadened. There was no distinct difference in the length of the two legs. On discharge from the hospital, the mobility of the legs was normal. The left tibia was a little thicker than the right, but otherwise there were no abnormalities.

Re-examination on Sept. 12, 1946, showed no clinical abnormality. X-ray examination showed a slightly irregular epiphyseal line.

CASE 5.—A girl, born Nov. 20, 1945, was admitted to Queen Louise's Children's Hospital November 24 with a diagnosis of acute gastroenteritis with intoxication.

Weight at birth was 2,650 Gm. The child was extremely exhausted, and on November 26, because of edema of the brain, was given a bone marrow infusion of 10 c.c. 50 per cent glucose in the left tibia. Seven days later the entire left leg was red and swollen. X-ray examination on December 19 showed extensive osteomyelitis with focal destruction of the proximal metaphysis, a nut-sized area of rarefaction in the distal part of the diaphysis, and total necrosis of the entire diaphysis, which was enveloped by a vigorous sequestral capsule.

Under treatment with hot compresses and sulfathiazole the process became quiescent. On Feb. 28, 1946, no demonstrable abnormality of the left leg could be made out. One month later the patient died of an intercurrent disease.

Our series includes no instance of subcutaneous abscess formation, nor have we observed any instance of fat embolism as described by Wile and Schamberg.<sup>42</sup>

As is evident from the case histories above, the five instances of osteomyelitis arose in connection with (1) continuous infusion (Case 1), and (2) simple infusion of hypertonic solutions, namely, concentrated serum (Case 2), and 50 per cent glucose (Cases 3 to 5).

In the 944 bone marrow infusions of isotonic solutions (blood, serum, and bicarbonate) with employment of Køster's technique, osteomyelitis was not observed in any patient, in spite of the fact that many of the patients were extremely exhausted and, consequently, highly susceptible to infection.

In the future, a sharp distinction must be made between the risk of osteomyelitis after the simple infusion of isotonic fluids in one seance as given by Køster, and the risk after continuous bone marrow infusion and infusion of hypertonic fluids, which in our material has been about 13 per cent.

This conclusion, we think, is the important finding of our study.

The risk implied by continuous bone marrow infusions is evident from the osteomyelitis literature cited, as in all the cases quoted the osteomyelitis developed after continuous infusion.

Attention has been called from other sides to the irritative effect of the hypertonic solutions. Experimentally, Wallden<sup>41</sup> has demonstrated roentgenographic changes after such infusions, and Christiansen<sup>10</sup> has seen rather considerable periosteal reactions after bone marrow infusions of undiluted contrast media.

#### CONCLUSION

It is generally agreed that blood transfusion performed on the proper indications is one of the most valuable therapeutic measures available. Infusion into the cubital, saphenous, cervical, or cranial veins is often difficult for experienced physicians; and even with the employment of certain technical tricks (Landman<sup>23</sup> and Isotalo<sup>19</sup>) it is often impracticable without laying the vein bare. Infusion into the longitudinal sinus is a measure about which the inexperienced physician always will feel uneasy. (In going through about half a hundred case records where this form of infusion was employed, we have found two cases in which a subdural hematoma developed, one of which required operative treatment.)

According to our experience, there can be no doubt whatever that the introduction of the technique of bone marrow infusion in pediatrics has been of valuable significance.

On the other hand, however, as already pointed out by Tocantins and O'Neill<sup>26</sup> in their first paper, and more recently emphasized by Wallden,<sup>41</sup> it has to be kept in mind constantly that bone marrow infusion is not meant to replace intravenous infusion. It is a supplementary method, and it should be reserved for patients in which the intravenous way is not suitable, as is often

true in children. Even though the bone marrow route absorptonally is analogous to the intravenous, intraosseous injection of the same substances may involve a considerable risk.

We think the most important result of the present study has been that it now seems quite evident that we have to distinguish sharply between the ordinary simple blood transfusion or infusion of isotonic solutions in one seance, which has proved to be quite safe so far, and the continuous infusion, or the infusion of hypertonic solutions that implies a considerable risk of osteomyelitis and subsequent disturbance in growth of the bone.

Consequently, we do not hesitate to employ the bone marrow infusion for simple blood transfusion in infancy. In about 10 per cent of the cases, however, there will be technical difficulties in placing the cannula properly, but only in 2 per cent of the cases will these difficulties be so great as to make the transfusion altogether impossible. Furthermore, we have never seen any unfortunate consequences from unsuccessful attempts at transfusion in this way.

When it comes to continuous infusion, the requirements as to aseptic and antiseptic precautions, technique, and apparatus will be far more exacting. The infusion fluid must be kept absolutely sterile, and there must be no possibility of airborne infection. These requirements are met by the English "Transfuso-Vac" system<sup>2</sup> and the apparatus constructed by Price and Tocantins,<sup>28</sup> just to mention a couple of examples. We have had no personal experience with these measures, but we find it advisable never to extend a continuous infusion beyond twenty-four hours (Køster, private communication).

As to the injection of hypertonic solutions via the bone marrow, we are decidedly against the employment of this measure. The only exception to this rule must be a vital indication under circumstances affording no possibility of laying a vein bare, e.g., in manifest edema of the brain or far advanced hypoglycemia. We also wish to remind that bone marrow infusion of hypertonic solutions is associated with very intense pain (Meyer and Perlmutter<sup>26</sup>), probably as a sign of tissue injury. Presumably it is through this tissue injury that ubiquitous bacteria, which usually are completely or partly apathogenic, have a possibility of exerting a deleterious effect, resulting in osteomyelitis.

We have emphasized these facts in order to contribute toward keeping the simple bone marrow transfusion, which offers great advantages in infancy, from falling into discredit. No dangerous, let alone fatal, complications have been observed in connection with its employment.

#### SUMMARY

1. Material is presented, on nearly 1,000 bone marrow infusions given to children, aged 0 to 4 years, chiefly to infants. The character of the material, frequency of infusions, and the fluids injected are shown in Tables I and II. The very simple technique is described in detail.

2. Histologic examination of the tibia, performed on eleven patients from one to fourteen days after bone marrow infusion, showed no abnormality, especially no damage to the epiphyseal line.

3. X-ray examination of the tibiae, performed on thirty-six patients from one to two years after bone marrow infusion, showed no abnormality of the bones.

4. According to our experiences from 686 infusions, ordinary simple blood transfusion via the bone marrow at one time is quite safe, as we never have seen it followed by any serious complication, let alone osteomyelitis.

5. Continuous infusion, or infusion of hypertonic solutions, implied a considerable risk of osteomyelitis. Five instances of this complication are reported.

6. In our opinion, the failure to emphasize these facts in the literature is likely to place the employment of blood transfusion via bone marrow in infancy in a false position.

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# THE ESTIMATION OF EXTRACELLULAR AND TOTAL BODY WATER IN THE NEWBORN HUMAN INFANT WITH RADIOACTIVE SODIUM AND DEUTERIUM OXIDE

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TRACER techniques have been used frequently for estimation of extracellular and total body water. In adult man there are extensive observations on the volume of extracellular fluid determined from the distribution of sodium tagged with its radioactive isotope,<sup>1</sup> and there is a single observation on the volume of total body water determined from the distribution of deuterium oxide.<sup>2</sup> We have been unable, however, to find any data of this kind for the newborn human infant. In addition to giving us essential information for current studies on the permeability of the human placenta, our observations, though limited to three cases, give consistent answers to the questions: what proportion of the body weight in the newborn is water and how much of this water is extracellular?

Sodium chloride, tagged by radioactive sodium ( $\text{Na}^{24}$ ) at intensities of radiation below those known to produce measurable biologic effects, was dissolved in water containing deuterium oxide ( $\text{D}_2\text{O}$ ) and injected into a scalp vein of three newborn human infants. Two and one-half to three hours later, samples of oxalated blood for analysis were obtained by internal jugular puncture. This period of time is sufficient for equilibration of heavy water ( $\text{DHO}$ ) in blood with extravascular water.<sup>2</sup> It is not sufficient for complete equilibration of injected sodium in adult man, but further time up to six hours after injection<sup>1</sup> results in an increment of volume of distribution which for our purposes is unimportant. Radioactivity of the plasma fraction of the blood was measured by a temperature-controlled, pressure ionization chamber connected to a string electrometer. These measurements were corrected for the error due to self-absorption of radiation by the wet plasma sample.<sup>3</sup> The water of the blood for measurement of its deuterium content was obtained by vacuum distillation to dryness. Purification of this water and the method of determining the concentration of heavy water by the falling drop method were as described by Keston, Rittenberg, and Schoenheimer.<sup>4</sup> The volumes of distribution of the injected sodium and deuterium oxide ( $\text{Na}$ -space or  $\text{DHO}$ -space) were determined from the formula:

$$V_2 = \frac{C_1 V_1}{C_2}$$

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where  $C_1$  and  $V_1$  are the concentration and volume of the substance intravenously injected,  $C_2$  the concentration at the end of two and one-half to three hours in plasma, if for sodium, or in the water extracted from whole blood, if for heavy water, and  $V_2$ , the final volume of distribution of the tracer in the subject. As is customary,  $V_2$  is expressed as per cent of body weight on the assumption that the density of the fluid of  $V_2$  is unity. The concentration of tagged sodium in plasma was obtained from the measured radioactivity, 1 mg. of sodium in these experiments having a radioactivity of  $2.43 \times 10^5$  counts per second. In the case of tagged sodium, no correction was made for water content of plasma, for sodium bound in the plasma, or for the Donnan effect.<sup>1</sup> Evidence that a satisfactory measure of total body water is obtained from the experiments with deuterium oxide has been reported by Moore,<sup>2</sup> who found good agreement in the rabbit between the values derived from deuterium oxide and those obtained by desiccation of the carcass.

Results are given in Table I. The average value of 74.6 per cent of body weight for total body water differs only slightly from that of 72.5 per cent reported for a single adult male by Moore<sup>2</sup> using the tracer technique and 75.5 per cent found by Iob and Swanson<sup>5</sup> by desiccation of a full-term human infant. Utilizing the data of Iob and Swanson<sup>5</sup> on the chloride content of a human infant at term, and assuming that chloride is almost completely extracellular, Harrison, Darrow and Yannet<sup>6</sup> have calculated the extracellular water to be 43 per cent of the body weight. This is in excellent agreement with the average value of 43.5 per cent obtained two and one-half to three hours after injection of labeled sodium, and indicates that choice of this period of time after injection in the newborn avoids relatively large distortion of the value for extracellular fluid due to penetration of labeled sodium into bone.<sup>6, 7</sup>

TABLE I

SUBJECT	AGE (DAYS)	WEIGHT (GM.)	Na* IN- JECTED (MG.)	C.C. 96% D <sub>2</sub> O INJECTED	Na* PER C.C. PLASMA (MG.)	% DHO IN PLASMA WATER	% BODY WEIGHT	
							Na* SPACE	DHO- SPACE
Baby C	6	3,990	7.14	6.0	0.00412	0.195	43.5	73.8
Baby E	7	3,010	4.48	5.0	0.00322	0.208	46.2	76.8
Baby S	1.5	2,920	4.48	5.0	0.00376	0.222	40.8	73.2
Average							43.5	74.6

Na\* refers to sodium tagged with radioactive sodium. The values for Na\* per cubic centimeter plasma and per cent of heavy water in plasma water were obtained on samples secured two and one-half to three hours after injection.

Considerable evidence is now at hand that the process of growth is accompanied by an increase in the ratio of the intracellular to the extracellular phase. Extracellular water in adult man, as determined with tagged sodium three hours after intravenous injection, constitutes 25 per cent of body weight.<sup>1</sup> The sodium-space in relation to body weight, as determined in these experiments, is 1.7 times as large in the newborn as in the adult, and constitutes 58 per cent of total body water in the newborn as compared to 35 per cent in the adult. Harrison, Darrow and Yannet,<sup>6</sup> using the chloride analyses by Iob and Swan-

son,<sup>5</sup> found that the extracellular fluid in the human fetus during the fifth month of pregnancy amounts to 62 per cent of body weight and that this value progressively decreases to term. Much the same results were obtained with the fetuses of guinea pigs using radioactive sodium;<sup>3</sup> the sodium-space two-thirds through gestation approximates 60 per cent of body weight and falls to about 30 per cent at term. Yannet and Darrow<sup>8</sup> in their study of tissues of the growing cat also observed a decrease in extracellular fluid volume from the fourth to the sixth month of postnatal life.

#### SUMMARY

On the basis of dilution of a known quantity of intravenously injected sodium chloride tagged with a radioactive isotope of sodium, the extracellular fluid volume in three newborn human infants has been found to average 43.5 per cent of the body weight. Similar measurements with deuterium oxide gave a volume of total body water equal to 74.6 per cent of body weight.

We are obliged to the Abbott Laboratories for a grant for purchase of the heavy water.

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## RENAL GLYCOSURIA ASSOCIATED WITH PENTOSURIA

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IT BECOMES apparent that the presence of a reducing substance in the urine must be considered critically when it is realized that one out of every six persons with a melituria suspected of diabetes is ultimately proved to have a benign condition.<sup>1</sup> It is unsafe, however, to assume that glucose is the actual cause of a positive reduction test, especially when the concentration of the reducing substance is less than 1 per cent, unless glucose is definitely identified. Demonstrating glucose should not exclude the possibility of a combination of two or more sugars existing concomitantly. An instance of renal glycosuria associated with intermittent pentosuria occurring together in the same patient presenting diabetic symptoms is being reported, accordingly, as a case in point.

### CASE REPORT

E. G., a 5-year-old Negro boy, was admitted to The Children's Memorial Hospital for study of a persistent melituria first noted at 26 months of age. The patient, one of three siblings, had been well except for a history of pertussis, varicella, exposure to tuberculosis, umbilical hernia, and hydrocele. There was no known family history of diabetes mellitus. There was nothing to suggest hepatic disease, hyperfunction of the endocrines, increased intracranial pressure, alkaptonuria, convulsions, or the prolonged use of drugs. The course had been benign although punctuated by a craving for sugar, polydipsia, and polyuria. Melituria, presumed to be a glycosuria, was almost constantly present, though occasional urine specimens taken before breakfast were free of sugar. Frequent quantitative determinations for reducing substances taken during the patient's observation in the outpatient department had varied from 0.16 to 0.77 per cent, the lower values occurring uniformly in the morning in a usual range of from 0.2 to 0.3 per cent. Active fermentation of afternoon urine specimens was the rule, though morning specimens often failed to evidence fermentation, even in the presence of reducing substances in a 0.2 to 0.3 per cent concentration. Acetone and diacetic acid were never demonstrated.

The dietary history was pertinent and revealing. The child ate cherries for breakfast daily during the months of June through December and was quite fond of plums, grapes, and berries, which were alternated at the morning meals during the rest of the year. Alterations in the diet with restriction of carbohydrate had been tried, moderately affecting the quantitative afternoon sugar excretion. The fruits noted, however, had never been eliminated from the diet.

Physical examination at the time of admission to the hospital revealed an alert, asymptomatic child, 43 inches in height and weighing 48 pounds. Aside from evidence of repair of an umbilical hernia and hydrocele, no abnormalities were demonstrable.

*Laboratory Observations.*—The blood count was normal. Reactions to an Eagle and Mantoux test (1:1,000 dilution) were negative. Analysis frequently repeated on several days revealed that the urine was normal except for a positive qualitative Benedict's reaction (1 to 3 plus) with quantitative values ranging from 0.25 to 0.75 per cent. Acetone and diacetic acid were never present. Postcibal morning specimens were negative when the fruits noted were eliminated from the breakfast meal.

Positive phloroglucinol-hydrochloric acid tests and positive orcin tests (Bial's modification) were obtained from urines excreted following a breakfast containing pentoses in moderate quantity. This phenomenon was not evidenced by other children on a similar

diet. Negative Rubner, Seliwanoff, and mucic acid tests of the urine were obtained. Characteristic pentosazones were obtained with the phenylhydrazine test.

An oral dextrose tolerance test, using 1.75 Gm. of dextrose per kilogram of body weight, yielded the following blood sugar levels after fasting (12 hours) and in one-half hour, one, two, and three hours respectively: 79, 117, 106, 98, and 83, mg. per 100 c.c. of whole blood. Urine samples collected just before drawing each blood sample were negative for reducing substances except at the end of one hour, when a 2 plus qualitative (0.5 per cent quantitative) Benedict's reaction was obtained.

An intravenous dextrose tolerance test<sup>2,3</sup> revealed the following capillary blood sugar levels after fasting (12 hours) and in one-half, one, and two hours respectively: 103, 129, 96, and 113, mg. per 100 c.c. of whole blood. Urine specimens collected before drawing each blood sample were sugar free except at one-half hour, when a 0.75 per cent quantitative reduction of Benedict's solution was obtained.

A pentose tolerance test, using 1.75 Gm. per kilogram of technical d-xylose was done.<sup>4</sup> At the intervals noted, 5 c.c. of blood were obtained by venipuncture and collected in oxalate bottles. The total blood sugar was determined by the Folin-Wu method. The nondextrose reducing substance was determined by the same method, removing fermentable sugar by fermentation in washed yeast cells.<sup>5</sup> The total blood sugar minus the nondextrose reducing substance represents dextrose. The pentose is derived as the difference between the fasting value for nondextrose reducing substance and subsequent values for nondextrose reducing substance obtained after pentose administration. The results are given in Tables I and II.

TABLE I. PENTOSE TOLERANCE TEST

TIME (HR.)	TOTAL SUGAR (MG./100 C.C.)	NON- DEXTROSE REDUCING SUBSTANCE (MG./100 C.C.)	DEXTROSE (MG./100 C.C.)	PENTOSE (MG./100 C.C.)	URINE VOLUME (C.C.)	PER CENT REDUCING SUBSTANCE IN URINE
<i>Patient</i>						
Fasting	95	15	80	0	75	0.1
$\frac{1}{2}$	122	48	74	33	15	0.3
1	145	65	80	50	15	1.6
2	166	84	82	69	37	5.0
3	130	64	66	49	38	4.5
<i>Control</i>						
Fasting	86	21	65	0	80	-
$\frac{1}{2}$	133	44	89	23	90	<0.1
1	169	70	99	59	20	0.13
2	190	92	108	71	67	0.14
3	200	90	110	69	110	<0.1

TABLE II. DIFFERENTIAL VALUE OF USUAL TESTS FOR IDENTIFICATION OF URINARY SUGARS\*

TESTS	GLU- COSE	GALAC- TOSE	LAC- TOSE	FRUC- TOSE	PEN- TOSE	GLYCULO- NATES
Benedict's	+	+	+	+	-	+
Fermentation	+	Occasion- ally, slowly	-	+	-	-
Bial's orcinol	-	-	-	-	+	+
Rubner's	-	-	+	-	-	-
Seliwanoff's	-	-	-	+	-	-
Mucic acid	-	+	+	-	-	-
Phloroglucinol	-	-	-	+	+	+
Naphthoresorcinol	-	-	-	-	-	+

\*The following chart is appended to indicate the differential value of the usual qualitative tests for identification of urinary sugars. The significance of the reactions elicited in the case being presented becomes more clear as reference is made to the chart. Positive and negative reactions are indicated by + and - respectively.

Control values were obtained from a child weighing 52 pounds. A dextrose tolerance test using 1.75 Gm. dextrose per kilogram of body weight yielded the following fasting (12 hours), one-half-, one-, and three-hour blood sugar values in terms of milligrams per 100 c.c. of whole blood: 86, 123, 120, 102, and 104. The urine specimens obtained concomitantly at the same intervals of time were negative for reducing substances. The non-protein nitrogen was 33 mg. and the urea nitrogen 15 mg. per 100 c.c. of blood. The pentose tolerance curve using 1.75 Gm. per kilogram of body weight of technical d-xylose yielded the values noted.

Other chemical determinations of the patient's blood were as follows: The nonprotein nitrogen was 29 mg., the urea nitrogen, 13 mg., creatinine, 1.1 mg. per 100 c.c. of whole oxalated blood. Other values per 100 c.c. of serum were calcium, 10.6 mg.; phosphorus, 3.4 mg.; phosphatase, 8 Bodansky units; cholesterol, 188 mg.; cholesterol esters, 94 mg. The bromsulfalein test, using 5 mg. of bromsulfalein per kilogram, revealed less than 5 per cent of the dye in the serum after 30 minutes. An intravenous pyelogram revealed normal findings.

#### DISCUSSION

The most frequent single disease entity characterized by glucosuria is diabetes. Diabetes mellitus is responsible, however, for only 30 per cent of clinical glycosurias in children.<sup>6</sup> Hyperglycemic glycosurias other than diabetes should, therefore, be given their due consideration. Hyperfunction of some of the endocrine glands (thyroid, pituitary, adrenals), chemical agents, hepatic and renal disease, acidosis, asphyxia (caused by anesthetics, shock, convulsions) and increased intracranial lesions or pressure should all be borne in mind. Normoglycemic glycosurias should suggest renal glycosuria and the clinically significant meliturias other than glycosurias, including the excretion of the disaccharides, lactose and maltose, and the monosaccharides, galactose, levulose, and pentose.

A variety of nonsugar reducing substances is demonstrable in human urine. Uric acid, nucleoprotein, creatinine, formaldehyde, and chloral reduce Fehling's solution, though their effect is less appreciable on Benedict's qualitative solution. Ascorbic acid in large dosage and homogentisic acid of the alkaptonuric reduce copper salts. Glycuronic acid, a conjugating substance in the detoxifying mechanism of the liver complementing hippuric acid and sulfate formation, constitutes a not uncommon urinary reducing substance. Glycuronic acid is found in the urine after liberal feeding of spinach, and in considerable quantity after the ingestion of a number of drugs including salicylates, antipyrine, amidopyrine, morphine, codeine, barbiturates, chloral, camphor, phenol, and menthol.<sup>7</sup> It is apparent, therefore, that care must be exercised in the interpretation of a positive reduction test, particularly when one of these nonsugar substances may be implicated.

In the ordinary course of digestion, carbohydrates in the diet are absorbed either as pentoses or hexoses. The pentoses are found widely distributed in nature, being present in polysaccharide combination as pentosans in the seeds, roots, stems, and leaves of all forms of plant life. Pentoses are present in the human body, the total content of human organs being estimated at about 10 Gm.<sup>8</sup> Pentoses, although important constituents of nucleic acid and certain intracellular enzymes, are not found in the body in a free state, however, except in the condition of pentosuria.

In considering melituria in children, pentosuria of the alimentary type must be borne in mind, for diets after 6 months of age are apt to contain large amounts of food rich in pentose such as prunes, plums, grapes, cherries, strawberries, blackberries, apples, and other fruits. Ingestion pentosuria is a temporary manifestation disappearing when pentose intake is limited. Johnstone<sup>9</sup> found that seventeen out of eighteen individuals who drank 1½ L. of apple juice were temporarily pentosuric. Joslin<sup>1</sup> likewise indicates that the ingestion of pentose-containing foods in large quantities prompts pentose excretion. In the case being reported, pentosuria occurred after servings moderate in quantity and probably not exceeding the usual assimilation limit as pentose was not present in urine of the two siblings on a similar diet. Glucose is actively and selectively reabsorbed in the proximal convoluted tubules, and hence does not ordinarily pass unhindered into the urine, while the threshold value for pentose is low. Considering the fact that our patient had an associated low threshold for glucose, it was not too difficult to assume that the threshold for pentose was likewise lowered. Pentosuria could, thus, conceivably occur on servings of a size not ordinarily causing a significant alimentary pentosuria.

When the concentration of pentoses in the urine is constant, unaltered by changes in the diet, and influenced only by the administration of drugs, a condition of chronic essential pentosuria exists. Essential pentosuria is considered as an inborn error of metabolism along with albinism, alkaptonuria, cystinuria, and porphyria. The incidence is rare and has been estimated as occurring in one out of 50,000 people.<sup>10</sup> Essential pentosuria is predominantly found in Jewish males and is believed to be inherited as a simple recessive characteristic. The disturbance is generally considered an innocuous asymptomatic metabolic anomaly, although associated symptoms of migraine and manifestations of the so-called vagotonic constitution have been described.<sup>11</sup> Experimentally it has been shown that young rats given a diet containing 35 per cent xylose developed cataracts in approximately the same time as litter mates receiving a diet containing 35 per cent galactose.<sup>12</sup> There have been clinical instances of cataracts reported in galactosuria<sup>13, 14</sup> but none noted in pentosuria.

Pentosuria with diabetic symptoms has been described in an infant 22 months of age presenting a picture of polyphagia, polydipsia, polyuria, and pollakiuria.<sup>15</sup> Levy's case<sup>16</sup> also suggested diabetes in view of a history of weight loss, pallor, and a large output of urine. Essential pentosuria may not only be confused with diabetes mellitus, but may actually occur with it. Voit<sup>17</sup> found a pentosazon in the urine of twelve of fourteen patients with diabetes. A similar concomitance has been noted by other observers.<sup>18-20</sup> Joslin and associates<sup>2</sup> were able to find only one questionable instance of such an association. The concomitance is apparently coincidental for pentosuria and is not related to a disturbed glucose metabolism or to variations in dietary carbohydrate. In most cases of diabetes the metabolism of xylose is likewise normal.<sup>21</sup>

While diabetes and pentosuria are etiologically distinct, their occasional clinical concomitance emphasizes the importance of not only identifying urinary constituents but of ascertaining the circumstances of that excretion. Failure to

recognize both when existing together is dangerous. Insulin dosage based on the urinary sugar is misleading, pentose being excreted constantly and independently of insulin and the blood glucose level. In a diabetic subject a confusing picture of melituria in the face of a normal blood sugar and clinical control, should, therefore, suggest the presence of pentosuria or an associated renal glycosuria.

Renal glycosuria is the usual diagnosis preceding the identification of pentosuria. Lasker and Enklewitz<sup>22</sup> described pentosuria occurring in twins, a case previously mistaken for juvenile diabetes mellitus and later for renal glycosuria. Both renal glycosuria and pentosuria are asymptomatic disease entities, often familial, benign in their course, and showing no tendency to progress toward diabetes. Both yield normal fasting blood sugar values, glucose, and pentose tolerance curves. Renal diabetes is associated with the excretion of a fermentable hexose. The renal function as a whole is normal,<sup>23-25</sup> though tubular reabsorption of glucose is diminished. Pentosuria, on the other hand, is associated with the excretion of a nonfermentable 5 carbon monosaccharide. Pentosuria is ascribed to an abnormal enzyme system which decarboxylates glycuronic acid and converts it into xyloketose. A fermentation test should be of value in helping to identify the two meliturias as independent entities, but certainly not when they occur together. Recorded instances<sup>26, 27</sup> of renal glycosuria associated with pentosuria are accordingly infrequently reported, probably due to the fact that a possibility of a combination of excreted sugars is not considered too often.

In the case being reported, a combination of sugars was suggested by conflicting fermentation reports. Negative fermentation studies on urines obtained shortly after breakfast and yielding a positive qualitative Benedict's test (0.3 to 0.4 per cent quantitative) were reported on several occasions, while late afternoon specimens fermented strongly. The observation that postcibal morning specimens contained a nonfermentable reducing substance not obscured by a fermentable reducing component occurring later in the day suggested that the former was probably contained in quantity in the breakfast meal. Pentosuria seemed likely in view of the regularity of ingestion of moderate quantities of pentose containing foods. Lactose and galactose, also nonfermentable sugars, were excluded on the basis of the tests outlined. Bial's modification of the orcin test was positive for pentose. The pholoroglucinol test was confirmatory for a pentose. With the phenylhydrazine test, crystalline osazones precipitated out in a yellow, flaky mass composed of long, yellow, needle-shaped crystals characteristic of pentasazons. Their appearance was identical with that of the osazones obtained from a known sample of pentose. The oral glucose tolerance curve excluded diabetes mellitus, suspected because of the diabetic symptomatology. The collected urines demonstrated a low renal threshold for glucose. The intravenous glucose tolerance test, apparently applicable to infants and children<sup>3</sup> ruled out hepatic disease, as did the other liver function tests indicated. Intravenous pyelograms and normal values for nonprotein nitrogen, urea nitrogen, and creatinine indicated good kidney function. The pentose tolerance curve was similar to that seen in nor-

mal persons.<sup>4</sup> While the output of ingested pentose by a pentosuric lasts somewhat longer and is slightly greater than in a normal person, the blood pentose and glucose tolerance curves are similar.

Other laboratory procedures are applicable in identifying pentoses. Urines containing pentose reduce Benedict's qualitative solution at 50 to 60° F. in ten minutes, while urines containing as much as 4 per cent glucose fail to cause a reduction.<sup>28</sup> A pentose urine retains its reducing power at room temperature almost indefinitely, while a glucose urine will show greatly reduced reduction under the same conditions. dl-arabinose and glycuronic acid do not reduce Benedict's qualitative solution in the cold or at 55° F. An aniline acetate paper test is a good confirmatory test for pentose.<sup>29</sup> When very small amounts are suspected, increased elimination and identification may be elicited by the administration of pyramidon or the previously indicated drugs. The melting point of osazones is not a simple or necessary routine procedure but can be done for absolute identification.

#### SUMMARY

An instance of renal glycosuria and pentosuria occurring together in the same patient presenting symptoms of diabetes mellitus is reported. The importance of recognizing pentosuria occurring in a diabetic patient is emphasized. The laboratory procedures necessary for the identification of the disease entities are simple, available, and easily interpreted, and are accordingly indicated.

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# POISONING DUE TO INGESTION OF WAX CRAYONS

## REPORT OF A CASE

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**R**EPORTS of aniline dye poisoning among infants are fairly numerous.<sup>1-6</sup> With the exception of one of the cases reported by Zeligs,<sup>2</sup> all of the patients have been infants poisoned by contact with diapers freshly stamped with material containing the aniline dye. The one exception among Zeligs' patients was a child who inhaled fumes from an aniline-containing material used to exterminate bugs.

The case reported here is that of a 38-month-old child who, after ingestion of wax crayons, developed symptoms of paranitraniline poisoning.

### CASE REPORT

*History.*—The parents stated that at 6:30 A.M., June 22, 1946, the child, H., appeared quite normal when she awoke, and was talkative, responsive, and active. She was taken to the bathroom and returned to bed. She and her twin sister were dressed in bathrobes and slippers, and allowed to look at books in bed and to play alone in their room, as had been their custom. They were in a large, sunny nursery, containing nothing but the usual type of children's toys.

At 8:30 A.M., when their door was opened, the twins were both playing with a large box of crayons which they had obtained by climbing up to the top shelf of a closet. Many of the crayons were broken and stepped upon on the floor, and several showed evidence of having been chewed. H. was sitting in the middle of the floor, her pajamas off, very subdued and still, in marked contrast to her sister. Her skin was bluish, her fingernails and toenails deep blue, and her lips and mouth black. Her respirations were rapid. She did not talk when questioned, but her twin sister said, "She ate crayons." The mother thought at first that the child might have been chilled, despite the warm morning. However, she did not respond to being blanketed and, when lying in bed, had considerable difficulty in breathing, turning, twisting, and trying to sit up. Her respirations became increasingly rapid and labored, and her color increasingly worse. She was brought to the doctor's office at about 9 A.M.

*Physical Examination.*—The patient was very weak and listless, but mentally clear. The rectal temperature was 100° F., respirations 20 and pulse 180 per minute. The skin was slate colored, while the nailbeds and lips were almost black. The abdomen was negative, but the heart seemed enlarged to percussion. The mouth and throat were negative except for the extreme cyanosis. The eyes, ears, and nose were normal. There was nothing abnormal on neurological examination, except that the child was listless and sluggish.

The patient was rushed to the hospital, oxygen was administered immediately, and 1 cat unit of digitalis was given hypodermically. Her condition had improved after about an hour, and it was decided to have x-ray films made of the stomach for evidence of the crayons, and of the heart for size.

*X-ray Report.*—"There is a quantity of opaque material in the stomach and right lower quadrant. Heart and lungs are normal." (Fig. 1.)

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The patient became quite dyspneic and more cyanotic in the x-ray department, but improved perceptibly upon being returned to the oxygen tent. Improvement was gradual and oxygen was discontinued after thirteen and one-half hours. Other therapy consisted of parenteral administration of fluids, repeated enemas and laxatives, and gastric lavage. Pieces of crayon were obtained by the latter procedure and these, together with the stomach washings, were saved for chemical study. The child's condition improved steadily and she was discharged from the hospital forty-eight hours after admission. She was below normal in general activity and health for at least two weeks following the poisoning episode.

**Laboratory Findings.**—On June 22, 1946, hemoglobin was 12.5 Gm.; red blood cell count, 4,560,000; white blood cell count, 10,900; neutrophils, 63 per cent; lymphocytes, 35 per cent; and monocytes 2 per cent. Urine showed a strong reaction when tested for acetone and diacetic acid. On June 24, hemoglobin was 12 Gm.; red blood cell count, 4,440,000; white blood cell count, 8,750; neutrophils, 43 per cent; lymphocytes, 54 per cent; monocytes, 2 per cent; basophiles, 1 per cent. Urine was the same as on June 22.

The remainder of the laboratory examinations were done by one of us (H. B.).

**Urine:** Urine sampled eight hours after ingestion of the crayons contained bilirubin in the high amount of 2.2 mg. per 100 c.c. and urobilinogen more than twice the normal. One week later, 0.5 mg. per 100 c.c. bilirubin was found. The corresponding blood serum level was 0.5 mg. per 100 c.c.; direct reaction was negative.

The spectrophotometric examination of the urine did not indicate the presence of hemoglobin or methemoglobin.

Color reactions with Millon's reagent, ferric chloride, and bromine water were positive, thus indicating the presence of conjugated para-aminophenol (Table I).

**Blood:** The first blood pictures did not reveal significant changes. Further examination showed a moderate anemia which was disappearing after two weeks (Table II).

TABLE I. URINE FINDINGS

TIME AFTER POISONING	BILIRUBIN MG./100 C.C.	UROBILINOGEN DILUTION	PARA-AMINOPHENOL
8 hours	2.2	1:50	positive
24 hours	1.6	1:20	
1 week	0.5	1:20	
2 weeks	0.0	1:20	

TABLE II. BLOOD STUDY

TIME AFTER POISONING	HB (GM./ 100 C.C.)	RBC (MIL- LIONS)	RET. (%)	WBC	S (%)	E (%)	B (%)	L (%)	M (%)	BILIRUBIN		
										MG. 100/C.C.	DIRECT	
Day of poisoning	12.5	4.6		10900	63.0			35.0	2.0			
2 days	12.0	4.4		8750	43.0		1.0	54.0	2.0			
1 week	8.5	4.1		9800	42.5	6.5	1.0	46.5	3.5	0.5	negative	
2 weeks	10.0	3.9	2.7	8700	38.0	4.0	1.0	50.0	7.0			
											THYMOL TURBIDITY TEST	
3 months	11.6	3.8		8750	36.0	7.0		51.0	6.0		negative	

Hb = hemoglobin; RBC = red blood cells; Ret. = reticulocytes; WBC = white blood cells; S = segmented cells; E = eosinophiles; B = basophiles; M = monocytes.

A blood sample, taken early enough to give evidence of methemoglobin formation, was not made available for examination.

**Stomach Contents:** The remnants of the crayons, removed from the stomach by lavage, weighed approximately 2 Gm.; they consisted mostly of red and orange pieces.

The stomach fluid was diazotized with potassium nitrite, beta-naphthol was added, and a red dye produced. The intensity of the color reaction proved the presence of appreciable amounts of primary aromatic amine.

*Wax Crayons:* A piece of red-orange crayon recovered from the vomitus was examined by a method used in the paint industry.<sup>7</sup> To one part of finely divided crayon, concentrated sulfuric acid was added; to another part, 10 per cent sodium hydroxide; and to a third part, saturated alcoholic potassium hydroxide solution. The reactions corresponded exactly to that of "light red paranitraniline."

The wax crayons used by the child and swept from the floor were "Crayola" crayons and "True Tone Crayons."



Fig. 1.—X-ray showing wax crayons in stomach.

#### EXPERIMENTAL STUDIES

In order to obtain information about this type of poisoning, additional examinations of wax crayons and animal experiments were conducted by one of us (H. B.).\*

1. Orange and red crayons were examined for parared, an organic pigment made by coupling diazotized paranitraniline with  $\beta$ -naphthol. The results of the examinations are shown in Table III.

Orange crayon and red-orange crayons (two brands) contained parared, while the red and the yellow-orange crayons were free of it. As expected, no parared was present in green, yellow, and white crayons.

\*With the assistance of Jeanne E. Mazur, M. A.

TABLE III. PARARED IN WAX CRAYONS

CRAYON	H <sub>2</sub> SO <sub>4</sub>	ALCOHOLIC KOH	70% HAC
Orange (B. & S.)	Positive	Positive	Positive
Red-orange (B. & S.)	Positive	Positive	Positive
Red-orange (T. T.)	Positive	Positive	Positive
Red (B. & S.)	Negative	Negative	Negative
Yellow-orange (B. & S.)	Negative	Negative	Negative
Green (B. & S.)	Negative	Negative	Negative
Yellow (B. & S.)	Negative	Negative	Negative
White (B. & S.)	Negative	Negative	Negative

2. To 10 c.c. samples of human gastric fluid (of different acidities), small amounts of finely divided red, red-orange, or orange crayons were added. These mixtures were shaken for one hour and then examined for parared. No parared was detected.

It was first assumed that the presence of primary aromatic amines would indicate degradation of the parared dye in the gastric fluid. The reaction for primary aromatic amine was positive in all instances. However, untreated gastric fluid also gave a positive reaction.

3. A small dog, weighing 9 kg., was fed approximately 3 Gm. of the orange crayon by stomach tube. The dog did not develop any signs of poisoning. The blood, which was free of methemoglobin before feeding the crayon, did not show methemoglobin either 2½ hours or 24 hours after feeding.

Another dog, weighing 15 kg., was fed approximately 4.5 Gm. of the orange crayon by stomach tube. The negative findings corresponded to the findings in the first dog.

A third dog, weighing 34 kg., received 6 Gm. of orange crayon through a stomach fistula. Likewise, in this experiment no clinical or blood changes were observed.

Urinalyses are shown in Table IV. There was no evidence of para-aminophenol.

TABLE IV. PARA-AMINOPHENOL IN URINE

REAGENT	COLOR REACTION	CONTROL (URINE AND P-AMINOPHENOL)
Dilute NaNO <sub>2</sub>	Pale yellow	Pale yellow
β-naphthol	Negative	Positive (green-brown)
5% phenol + NaClO	Negative	Positive (deep blue)
H <sub>2</sub> S Water	Negative (greenish)	Positive (deep purple)

All dogs received the crayon on an empty stomach.

In order to ascertain the toxic effect of para-nitraniline in our dogs, dog 1 was fed approximately 0.015 Gm. paranitraniline by stomach tube. The dog showed slight but definite signs of poisoning; methemoglobin was not found.

Our findings confirm that orange and red-orange crayons contain parared, the basic constituent of which is paranitraniline. However, the dogs did not show any signs of poisoning after ingestion of appreciable amounts of orange

crayon. This is in accordance with the general consensus that the finished dye is insoluble and harmless.

On the other hand, the case of poisoning herein reported was undoubtedly due to paranitraniline. We are, at present, still unable to explain the mechanism of the poisoning in this case. The finished dye does not contain an excess of free paranitraniline.

#### DISCUSSION AND CONCLUSIONS

The clinical and biochemical findings in our case are identical with those described in acute, and especially in acute industrial paranitraniline poisoning.<sup>8-12</sup>

The crayons ingested by the child were evidently the source of the poisoning, since she did not have access to any other material that could have caused the symptoms observed. The red-orange crayon used by the child was found to contain parared, an organic pigment made by coupling diazotized paranitraniline with beta-naphthol.

Poisoning in industry has been due to paranitraniline itself. The developed dye (parared) as contained in wax crayons, is supposed to be insoluble. In our case, para-aminophenol, an intermediate oxidation product of aniline in the body, was found in the urine. The positive amine reaction in the gastric fluid is not, however, of specific significance, since we ascertained later that normal gastric fluid gives this reaction.

Poisoning through ingestion of paranitraniline is "exceptional," according to the literature.<sup>11</sup> The fact that our patient had not taken food or liquid for at least twelve hours preceding the ingestion of the crayons was probably important. In Lehmann's<sup>13</sup> experiments, cats and rabbits with full stomachs tolerated much more paranitraniline than animals with empty stomachs.

#### SUMMARY

Severe poisoning of a 3-year-old child through ingestion of wax crayons was described.

Clinical and biochemical findings were identical with those reported in industrial paranitraniline poisoning.

A piece of red-orange wax crayon recovered from the vomitus was examined chemically. It contained parared, an organic pigment made by coupling diazotized paranitraniline with beta-naphthol.

Conjugated para-aminophenol, an intermediate oxidation product of aniline in the body, was found in the urine.

Parared is used also in painting toys.

Animal experiments were conducted by one of us (H.B.) to obtain additional information about the nature and mechanism of this type of poisoning.

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## DOUBLE AORTIC ARCH

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**A**NOMALIES of the aortic arch and its main branches were long considered interesting incidental post-mortem findings, clinically insignificant and of interest mainly for the light they shed on the normal development of the human arterial system. In reporting a case of double aortic arch found in a dissecting room specimen, a male aged 67, Lockhart (1929)<sup>1</sup> used the following phrase which was typical of the general attitude: "The whole interest of such a specimen lies in the fact that it stands as a milestone of striking and historic architecture upon the byways of development."

In 1837, Von Siebold<sup>2</sup> wrote of an infant who died at the age of 10 days, having had respiratory stridor, dyspnea, and cyanosis since birth. In addition to an interauricular septal defect and complete transposition of the great vessels, the infant had a complete double aortic arch which Von Siebold believed to have been the cause of the infant's marked stridor and dyspnea while feeding.

Buschendorff (1917),<sup>3</sup> Schleussing (1925),<sup>4</sup> and Ewald (1926)<sup>5</sup> each described one case, and in each, the symptoms and signs were almost identical. Since early infancy each patient had suffered from respiratory stridor, paroxysmal dyspnea, particularly during feeding, and ultimate death from asphyxia, despite x-ray treatment of a suspected enlarged thymus. Death in these infants occurred at the ages of 6 weeks, one month, and 5 months, respectively. Each was found post mortem to have been suffering from tracheal and esophageal compression by a double aortic arch.

Harris and Whitney (1927)<sup>6</sup> reported the case of a boy who had cyanosis and inspiratory stridor since birth and who died at the age of 19 months. In addition to an interventricular septal defect and complete transposition of the great vessels, a double aortic arch which was believed to be constricting the trachea was found at autopsy. Hermann (1928)<sup>7</sup> performed an autopsy on a 6-month-old infant who had suffered from cough, stridor, intermittent cyanosis, and head retraction since 2 months of age and found a double aortic arch encircling and constricting both the trachea and esophagus.

In 1933, Snelling and Erb<sup>8</sup> had a similar patient who had inspiratory stridor and respiratory difficulty during feedings since birth. Cyanotic attacks began at the age of 3½ months, at which time a barium swallow showed posterior compression of the esophagus at the level of the third and fourth dorsal vertebrae. The authors had a personal report from Blackfan<sup>9</sup> of a 5-month-old infant who died with similar symptoms and signs, and was found post mortem to have a right aortic arch with a persistent left ligamentum arteriosum causing tracheal and esophageal obstruction. Because of the similarity of the cases, a diagnosis of right aortic arch was made by Snelling and Erb in their case. However, when the infant died at the age of 4 months, the cause of respiratory dis-

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ress was found to be a constricting vascular ring made up of a double aortic arch. In these cases the symptoms and signs were identical and similarly produced, but in the first the constricting vascular ring was formed by the right aortic arch and left ligamentum arteriosum, while in the second it was formed by a double aortic arch.

Arkin (1926)<sup>10</sup> made a diagnosis of double aortic arch in six living adults, and in two cases the diagnosis was later confirmed at autopsy. These diagnoses were roentgenologic and accidental, in the sense that they were made in persons who were under investigation for symptoms unrelated to their vascular abnormalities.

Increasing cognizance was given to the syndrome produced by constricting vascular ring in infants, i.e., stridor, respiratory difficulty particularly while feeding, cyanotic attacks, and frequent head retraction. However, it remained as an academic diagnostic possibility, since no treatment was considered possible. Jex-Blake (1926)<sup>11</sup> described a puppy who suffered from increasing stridor and dysphagia. At autopsy the trachea and esophagus were found to be constricted by a right aortic arch and the ligamentum arteriosum attaching it to the left pulmonary artery. It was suggested by the author that surgical therapy in such a case would have been simple had the correct diagnosis been made. Not until 1939 was any further written suggestion made of therapy in such cases. Wolman (1939)<sup>12</sup> reported the case of a 4-month-old infant who died with the syndrome which we have outlined as typical of a constricting vascular ring. These symptoms were not relieved by irradiation of the thymus and no evidence of a mediastinal tumor was found. Autopsy revealed tracheal and esophageal compression by a double aortic arch. Wolman reviewed the previous reports of this syndrome and suggested that such patients would be susceptible to surgical treatment if an antemortem diagnosis could be made.

Schall and Johnson (1940)<sup>13</sup> reported the case of a 6-month-old infant who had the typical syndrome for four months before death. Bronchoscopy showed a constriction of the trachea at the carina, and dyspnea was relieved during bronchoscopy. Surgery was not attempted, and at autopsy a double aortic arch was found to be the constricting agent.

Maude Abbott (1931),<sup>14</sup> in a study of 1,000 cases of congenital heart disease, described five cases of double aortic arch, in two of which there were symptoms. Blackford and associates (1932)<sup>15</sup> wrote a complete discussion of congenital aortic anomalies, considering their embryologic etiology in particular. Blincoe and associates (1936)<sup>16</sup> compiled an even more complete bibliography of these conditions, prompted by their finding of an unsuspected double aortic arch in a post-mortem examination of an adult. Of forty cases of double aortic arch in the literature, they found that seven were in fetuses or infants who died in early life, twelve were accidental findings in adults, seven were poorly described, and twelve were asymptomatic adults, but in these there was a persistent right aortic arch and vestigial cords only of the left arch. Herbut (1943)<sup>17</sup> reviewed the congenital aortic anomalies found in 5,800 consecutive autopsies. He found no cases of tracheal or esophageal compression by right aortic arch with persistent left ligamentum arteriosum nor of symptoms from an anomalous right



subclavian artery. Of the two cases of double aortic arch, one was in an asymptomatic adult and the other was a 2½-month-old infant who had stridor, dyspnea, and cyanosis from birth.

In most of these reports of double aortic arch, the right (posterior) arch which runs behind the esophagus is described as being larger than the left (anterior) arch and running at a slightly higher level. In both of Arkin's cases there was a partial atresia of the left arch, which he incorrectly assumed to be the rule when a double aortic arch persisted. In the forty cases reviewed by Blincoe and associates,<sup>16</sup> only two patients were found to have the left arch larger than the right. In the single case reported by Schall and Johnson<sup>13</sup> the two arches were identical.

In all those reports in which the aortic branches are mentioned, each aortic arch is described as giving rise separately to its appropriate common carotid and subclavian arteries. In fact, the right (posterior) arch has two branches, the right common carotid and subclavian arteries; similarly, the left common carotid and subclavian arteries arise from the left aortic arch. In a few cases the right arch gives rise to a small vertebral artery, and in a few a patent ductus arteriosus or ligamentum arteriosum joins the left arch. In none of these cases is a right or left innominate artery described. Herbut<sup>17</sup> states categorically, "There is no innominate artery."

It may seem that undue emphasis is being laid upon the typical syndrome produced by a constricting vascular ring and the uniformity of the anatomic findings in the majority of cases. The condition of double aortic arch is of particular interest now, however, inasmuch as surgical treatment of it has been initiated recently. Gross (1945)<sup>18</sup> published a report of the first case of constricting vascular ring correctly diagnosed and treated. The patient was first seen at 4 months of age with the complaint of wheezing since birth. Thymic irradiation had no effect on the symptoms. He was seen intermittently during the rest of the first year of his life, and had acute febrile exacerbations of dyspnea and stridor. When he was about one year old, investigations were carried out in an attempt to find the cause of these episodes of respiratory difficulty. Roentgen studies of the esophagus after a barium swallow revealed a posterior indentation and forward displacement of the esophagus at the level of the third to fourth thoracic vertebrae. Similarly, studies of the trachea and bronchi after lipiodol instillation showed a constriction of the trachea just above the carina, at the same level as the compression of the esophagus. A diagnosis of constricting vascular ring was made and an operation was performed. At operation a double aortic arch was found and the smaller (left) anterior arch was divided. The ligamentum arteriosum, which joined the anterior arch, was also divided. The right arch was described as giving rise to a right innominate artery. The infant was relieved of his symptoms and made an uneventful recovery. Faber (1945)<sup>19</sup> has described two patients aged 2½ months and 2½ years, who both had persistent stridor and were shown radiologically to have a right aortic arch. It is probable that both these children had a constricting vascular ring produced by the persistence of a left ligamentum arteriosum.

Such cases should prove even more amenable to surgical treatment than those of double aortic arch. I can find no record of symptoms being produced by a partially atretic left arch with a persistent right (posterior) arch, but there is no reason why this should not occur. During the past ten years there have been, in this hospital, autopsies on ninety-five children under 13 years of age who had congenital cardiovascular anomalies. Of these, four had a complete double aortic arch. There were no cases of other forms of constricting vascular ring.

Summaries of the case records of the four children with double aortic arches follow. In the first child, there were no signs or symptoms produced by the vascular ring. The case is being presented for its anatomic interest. The other three infants had a constricting vascular ring and are therefore of both clinical and anatomic interest.

#### CASE REPORTS

**CASE 1.**—D. B., a white female infant, was born at full term weighing 8 pounds, 9 ounces, after a normal pregnancy and labor. The infant was breast fed for one year and developed normally with no respiratory symptoms and no illness. The family history was noncontributory. At the age of 20 months a severe diarrhea developed, and two days after the onset, on Sept. 6, 1940, the patient was admitted to the Children's Memorial Hospital. The child was found to be in a serious condition, toxic, and dehydrated. Diarrhea was persistent, accompanied by vomiting and extreme toxemia. The stool culture was positive for *Shigella paradyseenteriae*. Despite intravenous fluids and daily blood transfusions from Sept. 11, 1940, the child's condition did not improve. On September 16, increasing abdominal distension was noted with dullness in the flanks, and a diagnosis of peritonitis was made. Intravenous sulfanilamide was given for twenty-four hours, but was discontinued because the white count fell to 1,600. The child died on September 20, after many rectal hemorrhages and the development of pulmonary congestion. At no time was there any stridor or cyanosis nor other evidence of respiratory obstruction. The clinical diagnosis was: (1) flexner dysentery, (2) peritonitis, and (3) bronchopneumonia.

**Necropsy Findings.**—The clinical impression was confirmed by the findings post mortem. There was an acute inflammation of the mucosa of almost the entire gastrointestinal tract, with gangrene of the terminal ileum and the colon. The gangrene extended through the entire wall of the transverse colon and perforation had occurred in its midportion, leading to a purulent peritonitis from which *Shigella paradyseenteriae* was cultured. In addition, there was generalized pulmonary congestion, with bronchopneumonia of the right upper lobe.

An unexpected finding was an anomaly of the aortic arch. The heart was of normal size and structure, the only abnormality being a small hemorrhage into the myocardium of the left ventricle. With the exception of the aortic arch and its branches, there were no vascular anomalies. Shortly after its origin, the aorta divided into an anterior and posterior arch, which encircled the trachea and esophagus and joined to form the descending aorta. Each arch gave rise separately to its respective common carotid and subclavian arteries. There was no innominate artery. A large patent ductus arteriosus joined the left arch. There is no record of the relative levels of the two arches nor of their size. The pathologic diagnosis was: (1) bacillary dysentery (Flexner), (2) acute purulent peritonitis, (3) double aortic arch, and (4) patent ductus arteriosus.

**CASE 2.**—D. M., a 4-month-old white female infant, was first seen in The Children's Memorial Hospital Nov. 21, 1942, and was admitted on that day. The infant was born at full term weighing 8 pounds, 2 ounces after a normal pregnancy and labor. Shortly after birth, she had three "blue spells," but had none since. She was a breast-fed baby and developed normally except that she had very noisy respirations, particularly when awake. The family history was noncontributory.

Five days before admission to the hospital, the infant developed a cough, fever, and listlessness. These symptoms got worse and when first seen she was in a state of collapse.

The temperature was subnormal, the extremities were cold, and respirations were rapid. There was marked perioral cyanosis. No abnormal chest findings were noted, although stridor was marked, and diagnosis was deferred. X-ray of the chest showed collapse of the upper and lower lobes of the right lung, and air seen anterior to the heart was interpreted as a pneumomediastinum. However, exploratory aspiration of the anterior mediastinum failed to yield any air. On the day of admission, a bronchoscopic examination was performed and external compression of the left main bronchus was noted, but the etiology was obscure.

The infant was kept in an oxygen tent where her color was good but her respirations remained noisy. The chest was partly fixed in the inspiratory position and there was emphysema of the left lung. Fluids were given intravenously, as were 0.5 Gm. sodium sulfathiazole every six hours and  $\frac{3}{4}$  grain aminophylline three times daily. Attempts at oral feeding produced marked respiratory distress with cyanosis. On November 23, 50,000 units of antipneumococcus serum type 14 was given because culture of the bronchoscopic aspirations yielded pneumococcus type 14. On November 24, 125 c.c. of whole blood were given intravenously. The white count ranged from 29,000 to 36,000, but the temperature remained normal until November 25, when it rose sharply and death ensued. The clinical impression was: (1) acute laryngotracheobronchitis, (2) atelectasis of the right upper and lower lobes, and (3) aspiration pneumonia.

*Necropsy Findings.*—The abnormal findings at post mortem on this well-developed, 14½ pound female infant were limited to the vascular and respiratory systems. The heart was of normal size and structure. The great vessels arose normally but, shortly after its origin, the aorta divided into two branches which encircled and compressed the trachea and esophagus before uniting to form the descending aorta. The right (posterior) arch gave rise separately to the right common carotid and subclavian arteries. The left (anterior) arch also had two branches, the left common carotid and subclavian arteries, and was joined by the left ligamentum arteriosum. The measurements and relative levels of the two arches were not recorded. No other vascular anomalies were noted.

The trachea was collapsed just above the carina and there was atelectasis of the right upper and lower and left lower lobes of the lungs. In the atelectatic lobes there was an early bronchopneumonia. The left upper and right middle lobes were emphysematous. The pathologic diagnosis was: (1) double aortic arch, (2) tracheal compression with atelectasis of three lobes and emphysema of the other two, and (3) early bronchopneumonia.

CASE 3.—M. W., a white female infant, weighed 6 pounds, 12½ ounces, when born at full term after a normal pregnancy and labor. The family history was noncontributory.

Shortly after birth she had two attacks of cyanosis, which did not recur, but she had persistently noisy breathing. A diagnosis of enlarged thymus was made, but no x-ray therapy was given. From birth the infant was a feeding problem. She had many formula changes and regurgitated most of them. She gained slowly but had no illness until two weeks before she was admitted to the Children's Memorial Hospital, when she developed a cough, fever, and irritability, respiratory distress, and diarrhea. She was brought to the hospital on Feb. 21, 1943, in an apparently moribund state, with a temperature of 106° F., deep cyanosis, and slow, gasping, noisy respirations. There was suppression of the breath sounds on the right side, with a pause after inspiration. The infant was placed in an oxygen tent and was given Coramine and adrenalin at once, followed by intravenous fluids and 3.85 grains of sulfathiazole every four hours orally. An x-ray of the chest showed atelectasis of the right upper lobe and emphysema of the left lower lobe which was thought to be obstructive, but bronchoscopy was not done because of the infant's serious condition. One hundred cubic centimeters of whole blood were given intravenously on Feb. 22, but a bloody diarrhea and bleeding from the nose and mouth developed. The infant died on the third hospital day. The clinical impression was (1) right bronchopneumonia and (2) diarrhea.

*Necropsy Findings.*—Abnormal findings were limited to the vascular and respiratory systems in this infant also, but the baby was not so well nourished as the previous one. The heart was of normal size and structure, with the greatest vessels arising in the usual way.

However, the aorta divided into two arches, the larger running behind the esophagus and the smaller crossing in front of the trachea before they joined to form the descending aorta. The trachea and esophagus were constricted by this vascular ring. The smaller, left arch was joined by a fine patent ductus arteriosus and gave rise to the left common carotid and subclavian arteries. The two branches of the right arch were the right common carotid and subclavian arteries. There were no other vascular anomalies.

The upper lobe of the right lung was atelectatic, and the middle lobe was congested. The left lung was emphysematous. The pathologic diagnosis was: (1) double aortic arch, (2) atelectasis of right upper lobe, (3) congestion of right middle lobe, and (4) emphysema of left lung. The last of the four cases we are reporting is particularly illuminating.

CASE 4.—D. Z., a white male infant, was born at full term after a normal labor with a birth weight of 8 pounds. His mother had been diabetic since childhood, but the pregnancy, her second, had been uneventful. Her first pregnancy ended after seven months, and the male infant died, at the age of 3 months, of congenital heart disease. Otherwise, the family history was noncontributory.

The baby was in oxygen for some time after birth but went home at 3 weeks of age. He was well until 5 weeks of age, when his mother first noticed noisy and difficult breathing which was worse while feeding or lying. The stridor became worse, and attacks of cyanosis became so frequent that the baby was hospitalized at the age of 7 weeks. A diagnosis of aspiration pneumonia was made, and the baby remained in the hospital until he was transferred to the Children's Memorial Hospital on June 29, 1946, at the age of 4 months.

On admission, the infant weighed 15 pounds, 2 ounces. He was well developed and well nourished, having marked inspiratory stridor with substernal and supraclavicular retractions, but no persistent cyanosis. He was at first kept in an oxygen tent, however, because when they did occur, his attacks of cyanosis were alarmingly severe.

Roentgenograms of the chest showed no mediastinal tumor but a moderate upper mediastinal widening which was interpreted as an enlargement of the thymus but which did not diminish after thymic irradiation.

On June 30, a bronchoscopic examination was made and a high-grade compression stenosis of the trachea, at the carina, and of both main bronchi was seen.

On July 3, x-ray study of the esophagus after a barium swallow showed no abnormality, but a tentative diagnosis of constricting vascular ring had been made, and on July 12 another bronchoscopy was done. The same compression was seen; the stenosis was dilatable, but collapse recurred immediately on withdrawing the bronchoscope. The infant had such severe respiratory distress that an examination of the tracheobronchial tree after lipiodol instillation was not considered safe.

The infant continued to have one or more severe attacks of cyanosis each day, usually during or just after feeds, but between these episodes he was comfortable out of oxygen. During each one of these periods of cyanosis it seemed as though death was imminent, but aspiration and oxygen relieved him.

On July 25, lipiodol was given by mouth, and on fluoroscopic examination the material was seen to hesitate at the level of the third intercostal space, at which level posterior esophageal compression was noted. A diagnosis of constricting vascular ring was made, and, on July 27, an exploratory thoracotomy was performed.

*Operative Note.\**—Under cyclopropane anesthesia, the left pleural cavity was opened anteriorly through the third interspace. The third and second ribs were cut at the sternal margin. Adequate exposure was obtained with a rib-spreader. The mediastinal structures were exposed through a longitudinal incision in the mediastinal pleura lateral to and parallel with the phrenic nerve. The ductus arteriosus was found to be obliterated. The arch of the aorta appeared normal in size and position. The innominate left common carotid and left sub-

\*The Surgeon was Willis J. Potts, M.D.

clavian arteries apparently arose from the aorta in their usual normal positions. There was no evidence of a vascular ring or any other abnormality. The mediastinal pleura was repaired and the chest closed. The ribs were apposed with three catgut sutures encircling adjoining ribs, the second and third ribs were sutured to their sternal margins and the muscles sutured with catgut. As the last suture was put in the muscles of the chest wall, negative suction was made on a catheter in the pleural cavity to reexpand the lung. The skin was closed with silk. The child left the operating room in good condition.

After operation the infant did well and remained afebrile. There was good pulmonary aeration and no cyanosis. However, on the evening of the third postoperative day, he had a sudden, particularly severe attack of cyanosis in which he died.

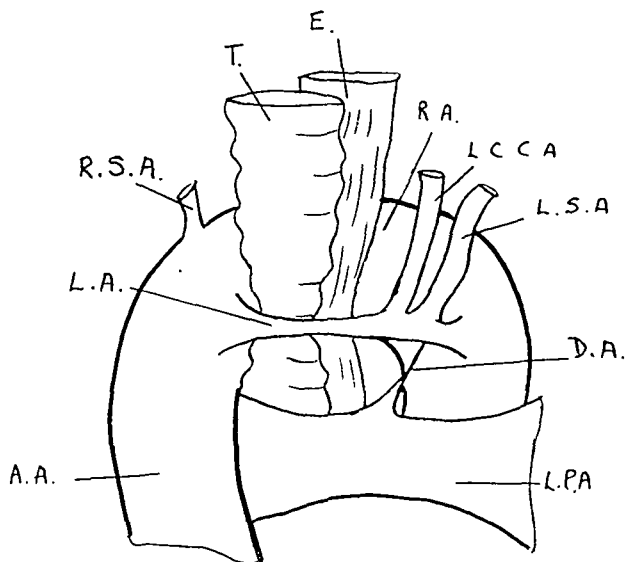


Fig. 1.—Composite diagram illustrating the usual anatomy of double aortic arch, anterior view.

- A.A., ascending aorta.
- R.A., right (posterior) aortic arch.
- L.A., left (anterior) aortic arch.
- R.S.A., right subclavian artery.
- L.C.C.A., left common carotid artery.
- R.C.C.A., right common carotid artery.
- L.S.A., left subclavian artery.
- D.A., ligamentum arteriosum or ductus arteriosus.
- L.P.A., left pulmonary artery.
- T., trachea.
- E., esophagus.
- R.V., right vertebral artery.

**Necropsy Findings.**—Once again the abnormal findings were limited to the vascular and respiratory systems. The infant was well nourished and well developed. The heart was normal in all respects, as was the vascular system with the exception of the aorta. The ascending aorta divided into two branches, which encircled and constricted the trachea and esophagus, and united to form the descending aorta. The left arch was the normal size of the aorta and lay slightly higher than the smaller posterior (right) arch, obscuring it from the anterior aspect. Each arch had two branches, the respective common carotid and subclavian arteries. There was no ductus arteriosus and no innominate artery, though the latter was simulated by the origin of the smaller, right arch. The lungs showed generalized congestion, with no atelectasis or infection. Pathologic diagnosis was (1) constricting double aortic arch and (2) asphyxia.

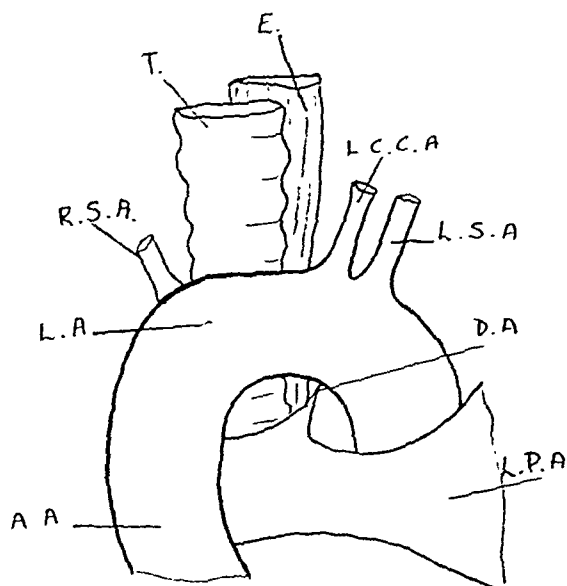


Fig. 2.—Anterior view of the double aortic arch in Case 4.

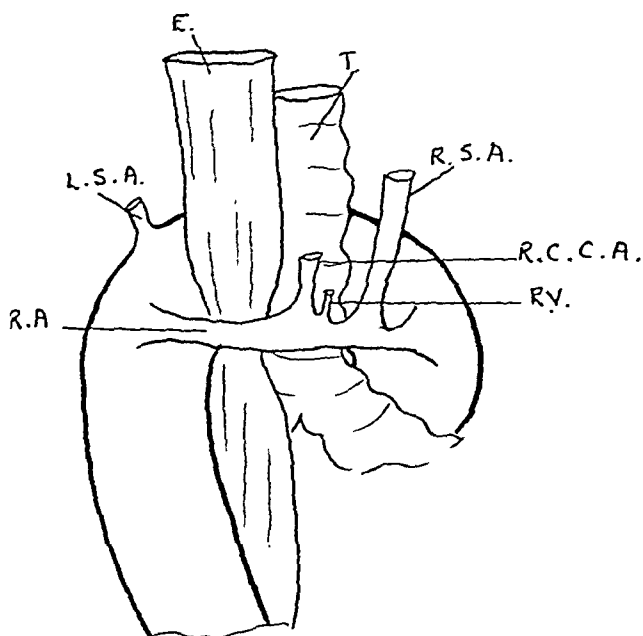


Fig. 3.—Posterior view of the double aortic arch in Case 4.

The particular importance of the last case is to emphasize that on rare occasions the usual anatomic structure of a double aortic arch is not found. The anterior arch may be both larger and higher than the posterior arch, obscuring the latter from the anterior aspect. This was the condition found in our last case. Also, with the exception of the case described by Gross,<sup>18</sup> I can find no record of a double aortic arch in which there was either a right or left innominate artery. In this case, what appeared to be the right innominate artery was actually the right subclavian artery, which arose from the posterior arch immediately after the aorta bifurcated.

It should be clear from the foregoing discussion that constricting vascular ring is not common, neither is it excessively rare. In particular, now that surgical therapy has been proved possible, the diagnosis should be borne in mind in cases of respiratory stridor in early life in which there are no laryngeal or tracheal abnormalities, no mediastinal tumor and no symptomatic response to irradiation of the thymus. The typical syndrome of constricting vascular ring has been fully re-emphasized in this paper, and the findings which corroborate the diagnosis are clearly set forth by Gross (1945).<sup>18</sup> Double aortic arch is by far the most common aortic anomaly to produce the typical syndrome, but it is important to realize that an identical syndrome can be produced by other anatomic abnormalities. A right aortic arch with persistent left ductus arteriosus or ligamentum arteriosum can form the constricting ring. Constriction of the esophagus, and sometimes of the trachea, is sometimes caused by the right subclavian arising from the descending aorta and running behind the esophagus. Similarly, the left subclavian may arise from a retroesophageal diverticulum of a right aortic arch and thus cause esophageal compression. These conditions are all fully considered by Gross (1946)<sup>20</sup> in an article dealing with the surgical approach to such abnormalities. In this paper we have considered only double aortic arch as a cause of constricting vascular ring because it is most common and because there have been three cases in this hospital in the last ten years, while there has been no case with symptoms produced by the other aortic anomalies encountered.

#### SUMMARY

A review is made of eleven reported cases of double aortic arch in infancy, with descriptions of four other instances occurring in The Children's Memorial Hospital in the past ten years. One of these four patients had no respiratory symptoms, but the other three and the ten previously reported each had the typical syndrome of respiratory stridor since early infancy, made worse by feeding or lying prone, attacks of cyanosis, and susceptibility to pulmonary infections. Many were treated for an enlarged thymus without success.

In view of the surgical therapy now possible, emphasis is laid on the anatomy of double aortic arches. In all except one of the thirteen cases in infants, the left (anterior) arch was smaller and lower than the right (posterior) arch. In only one case was an innominate artery described; in all the others each arch gave rise separately to its respective common carotid and subclavian arteries.

My thanks are due to Dr. Stanley Gibson for much help with this paper, to Dr. Willis J. Potts for permission to publish the last case, and to Dr. James P. Simonds for freedom to review the necropsy records of the Children's Memorial Hospital.

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## ACUTE MENINGOCOCCEMIA

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ALTHOUGH there is general appreciation of the fact that a transient bacteremia is often a concomitant finding in meningococcal infections, the extreme propensity of the meningococcus toward invasion of the cerebrospinal meninges has caused many physicians to lose sight of the fact that acute meningococcal septicemia without meningitis is rather frequently encountered. Such an infection was first described by Solomon<sup>1</sup> in 1902. Since that time there have been numerous reports describing one or more cases, and in some of the more recent general discussions of meningococcal infections<sup>2-7</sup> the clinical picture of acute meningococcal septicemia has been noted. There are several recent discussions of meningococcemia without meningitis, in which a number of cases have been discussed.<sup>8-12</sup>

In the period between Oct. 20, 1941, and Aug. 31, 1946, there have been 296 patients with meningococcal infections treated in the Gallinger Municipal Hospital. The general plan of treatment and the results obtained in patients with meningitis have been reported elsewhere.<sup>13-15</sup> The purpose of the present paper is to describe the clinical syndrome presented by the sixteen patients treated during this period because of a meningococcemia without meningitis.

The first of these patients was admitted to the hospital Oct. 25, 1941, the last on Aug. 3, 1946. Four patients were admitted during 1943, three each in 1944 and 1945, and five in 1946. The youngest patient was 2 months old, the oldest, 54 years. There were four patients who were less than 1 year, two from 1 to 9, seven from 10 to 19, and three over 20 years of age. There were six female and ten male, eight Negro and eight white patients.

The clinical picture presented by these sixteen patients followed one of two patterns. Fourteen patients had mild or moderately severe illness, and presented a similar picture; two had a severe fulminating infection. (Table I.) These two groups will be discussed separately.

### MILD OR MODERATELY SEVERE ILLNESS (CASES 1 TO 14)

*Clinical Features.*—The duration of illness at the time of admission varied from less than one to six days. Six patients entered the hospital after being ill only one day and eight came in after being ill from two to six days. The history revealed that headache, fever, vomiting, and joint pains were almost uniformly present. Headache, which was complained of by nine of eleven patients who were old enough to identify the symptom, was severe and constant, but not as excruciating as that which is usually present with meningitis. The three infants who were too young to complain of headache were extremely irritable. Ten

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of the fourteen patients had vomited. This was usually nonprojectile. Eight patients complained of vague, generalized, joint pains, and one 50-year-old man had severe purulent arthritis of his wrists and the joints of one foot.

Fever was noted in the history of thirteen patients. It was present at the time of hospitalization of all these patients, ranging from 101.0 to 105° F. The maximum recorded temperature was 104° F. or over in eight patients, between 102 and 104° F. in five, and 101° F. in one. It lasted from eight hours to eight days, with seven patients being afebrile within twenty-four hours, and seven patients running a fever for between two and eight days.

A skin rash was recognized prior to admission by only six patients, but was recorded in the physical examination of all fourteen patients. The type of rash found in patients with meningococcemia is of considerable importance, and should be sought for with great care. It has been described by many recent observers. In nine of our patients the major rash was a discrete, widely scattered, maculopapular eruption that showed maximal concentration on the trunk or on the extremities with approximately equal frequency. It was usually present also on the palms and soles. The individual lesions varied from 1 to 5 mm. in diameter, were slightly raised, and usually faded on pressure. They were quite comparable in appearance with the rose spots seen in typhoid fever, but were usually more numerous. In only one patient were there larger, more indurated skin lesions which did not fade on pressure and which resembled the lesions which have often been observed in patients with chronic meningococcemia.<sup>16-17</sup> Petechiae were present as an associated finding in two of these nine patients with a maculopapular rash. In both they were small and widely scattered. In one 10-year-old girl they were found after the maculopapular rash had faded completely. Five patients showed a petechial and purpuric rash of the type more generally seen in patients with meningococcal meningitis, without other cutaneous manifestations.

Other than the fever and skin rash, the most frequently noted physical finding was a generalized arthralgia or arthritis. This was present in eight patients. One patient demonstrated a slight swelling of his wrists and ankles, and six patients complained only of stiffness of the joints and pain on motion. This symptom was very transitory and disappeared rapidly. The patient with a purulent arthritis from which meningococci were recovered had severe symptoms with residual stiffness of the joints at the time of his discharge.

*Laboratory Data.*—The pertinent laboratory findings obtained in these patients are summarized in Table II. The meningococcus (*Neisseria intracellularis*) was recovered from cultured blood in thirteen of the fourteen patients. The organism was typed in eight instances, in five of which it was found to belong to Group I, in two to Group II, and in one to Group IIa. Satisfactory typing was not obtained in five instances. The diagnosis in the disease in the remaining patient was made by the demonstration of serum agglutinins against the Group I meningococcus. Seven cultures of his blood were sterile.

The hemogram showed very slight abnormalities in the twelve patients for whom it was recorded during the most acute phase of the illness. The white

TABLE I. CLINICAL FEATURES OF SIXTEEN PATIENTS WITH ACUTE MENINGOCOCCÆMIA

CASE	SEX	RACE	AGE (YR.)	DURATION OF ILLNESS AT ADMISSION (DAYS)	SYMPTOMS				RASH			TEMPERATURE	
					VOMIT-ING	ARTHI-RALGIA	FE-VER	OTHER SYMPTOMS	MACULO-PAPULAR	PETECHIAL	DURA-TION (DAYS)	MAX-IMUM (° F.)	DURA-TION (HOURS)
1	M	N	9	4	+	+	+	Sore throat	Extremities	0	N.R.*	102.6	8
2	F	N	10	1	+	0	+	Stiff neck, rash	Generalized	Few	3	104.0	12
3	M	W	11	6	+	+	0	Abdominal pain	Trunk	0	4	104.8	72
4	F	N	7	1	+	+	+	-	Trunk	0	N.R.	106.0	20
5	F	N	27	1	0	+	+	Chills, stiff neck	0	Generalized	N.R.	104.6	104
6	M	N	13	1	+	0	+	Chill	Trunk	0	N.R.	105.2	8
7	F	N	7/12	5	+	0	+	Irritability	Extremities	Few (later)	2	102.0	16
8	F	W	8/12	5	+	+	+	Irritability	0	Extremities	5	104.0	72
9	M	N	16	4	0	+	+	Lethargy	Generalized	0	8	104.6	192
10	M	N	2/12	4	+	0	+	Irritability	Face and legs	0	N.R.	102.2	24
11	M	W	16	2	+	+	+	-	Generalized	0	4	103.0	32
12	F	W	54	1	0	+	+	Dizziness	0	Few, sclerae and arms	2	104.0	48
13	M	W	10	1	+	0	+	Convulsion	0	Generalized (few)	4	101.0	16
14	M	W	50	5	0	++	+	Purulent arthritis	0	Generalized	6	102.0	96
15	M	W	10/12	1	+	+	+	Rash	0	Generalized	N.R.	108.0	Died
16	M	W	18	N.R.	+	+	+	Shock	0	Generalized	N.R.	103.2	108

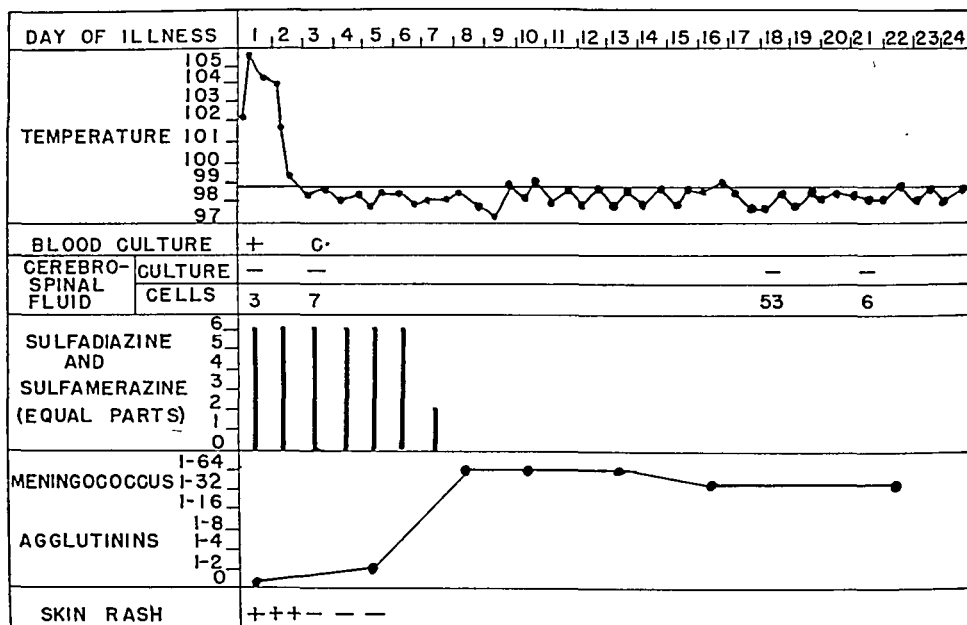
\*N.R. = no record.

TABLE II. LABORATORY DATA FOUND AND TREATMENT EMPLOYED IN SIXTEEN PATIENTS WITH ACUTE MENINGOCOCCEMIA

CASE	AGE (YR.)	BLOOD				BLOOD CULTURE MENINGO- COCCI		CEREBROSPINAL FLUID		FINDINGS	TREATMENT
		AGGLUTINATION		W.B.C.	DAY	TITER	RELATION TO BLOOD CULTURE				
1	9	N.R.*	N.R.	-	Group I	Not done	-	-	Supportive		
2	10	N.R.	N.R.	-	Group I	30 minutes before	-	Normal	Sulfadiazine		
3	11	7,060	N.R.	-	No group	At time of contaminated culture, 2 days before positive culture	-	Normal	Supportive		
4	7	11,500	16	1:64	Group I	One hour before	-	Normal	Supportive		
5	27	11,250	12	1:16	Group I	1 1/4 hr. before, 1 and 2 days after	-	Normal	Sulfadiazine and sulfamorzine		
6	13	10,500	7 & 12	1:64	No group	Same time and 2 and 19 days after 16 days after	-	53 cells	Sulfadiazine and sulfamorzine		
7	7 1/12	8,600	N.R.	-	No group	5 days after	-	Normal	Sulfadiazine and sulfamorzine		
8	8 1/12	7,600	N.R.	-	No group	Not done	-	-	Sulapyridine		
9	16	4,300	29	1:128	Negative	3 occasions during fever	-	Normal	Sulfadiazine		
10	2 1/12	12,050	N.R.	-	Group II	Not done	-	-	Supportive		
11	16	12,050	N.R.	-	Group II	Between 2 positive cultures	-	Normal	Sulfadiazine 2 1/2 hours after entry (day after spinal tap)		
12	54	N.R.	N.R.	-	Group I	Same time and 1 day after	-	Normal	Sulfadiazine day after entry (day after spinal tap)		
13	10	1,700	N.R.	-	No group	Same time	-	Normal	Sulfadiazine and sulfamorzine		
14	50	6,500	N.R.	-	Group IIa	Same time	-	Normal	Sulfadiazine and sulfamorzine		
15	10 1/12	25,000	N.R.	-	No group	Same time	-	Normal	Penicillin, sulfadiazine, and sulfa- morazine, plasma		
16	18	10,600 38,150	N.R.	-	Group I	Same time	-	Normal	Sulfadiazine, and sulfamorzine, plasma, penicillin, adrenal cor- tex extract		

\*N.R. = no record.

blood cell count ranged from 4,300 to 12,050 per cubic millimeter in these twelve patients and the differential count showed from 58 to 90 per cent cells of the polymorphonuclear series. In the patients with high granulocyte counts there was a moderate shift to the left in the Schilling index.



C\* = CONTAMINATED

Fig. 1.—Clinical course, treatment, and significant laboratory findings in a typical case of acute meningococcemia without meningitis (Case 6).

Blood serum agglutinins against meningococci were studied in four patients. All gave positive agglutinations, with titers similar to those reported for patients with meningococcal meningitis.<sup>18</sup> A graph of a typical agglutinin response as it occurred in Case 6 is shown in Fig. 1, together with the clinical picture. A single titer positive in a dilution of 1:128 was obtained on the twenty-ninth day of illness in the patient who showed skin lesions similar to those found in chronic meningococcemia. Titers positive to 1:64 were obtained on the seventh to twelfth days and the fourteenth day respectively in two patients, and 1:16 on the twelfth day in the fourth patient studied. The development of antibodies in patients with meningococcemia has been demonstrated also by Silverthorne<sup>19</sup> and Daniels.<sup>2</sup>

The spinal fluid was examined in one or more occasions in eleven patients. It was entirely within normal limits on each occasion, with the single exception of one patient (Case 6) who showed a pleocytosis with fifty-three cells per cubic millimeter on one occasion sixteen days after entry. Specimens of spinal fluid from this patient examined at the time of admission and two and nineteen days after entry were entirely normal, and since the patient was entirely asymptomatic it is probable that the pleocytosis noted was due to an error in the counting.

*Treatment.*—The only specific treatment used in this group of patients was the administration of one of the sulfonamides to ten. The other four patients responded to supportive care alone. Although they had maximal temperatures of 102.6, 104.8, and 106° F., they became afebrile after eight, twenty-four, seventy-two, and twenty hours respectively. Only one blood culture was obtained in the first two of these four children. In the third, the original culture was contaminated and the meningococcus was cultured from a blood sample drawn forty-eight hours after entry. The fourth patient had positive blood cultures obtained at the time of admission and on the following morning. The patients who were given sulfonamides usually responded very promptly to the customary doses of the drug, although the older patients as a rule required a somewhat longer time to become afebrile. Recovery was slow in the one patient with apparent chronic meningococcemia, with little real evidence of immediate benefit from the sulfonamide.

#### SEVERELY ILL PATIENTS

The two patients (Cases 15 and 16) with acute, fulminating meningococcemia each entered the hospital with an illness of twenty-four hours or less. They became ill with vomiting, fever, and prostration, developed widespread petechiae and purpuric lesions, and at the time of admission were in a state of shock. One of these patients showed a leucocytosis of 25,000; the other had a white cell count of only 10,600 on admission, but as he rallied from his shock the leucocytes numbered 38,150, with 76 per cent polymorphonuclears. Both of these patients had blood cultures positive for the meningococci, one belonging to Group I and the other being untypable. Both had normal spinal fluid findings with sterile cultures. Both patients were treated with massive doses of penicillin and sulfonamides in addition to the administration of parenteral fluids. One patient, who recovered after five days of fever, also received adrenal cortical extract. This was not available for the other patient, who died four hours after admission. The autopsy on the patient who died showed general visceral congestion but no adrenal hemorrhage.

#### COMMENT

One of the most significant features of this group of patients is that meningitis was not induced by lumbar puncture even when it was performed within a few minutes to an hour of the time when bacteremia was demonstrated by withdrawing blood samples containing meningococci from the patients. This sequence occurred in ten patients, including the fourth untreated patient described above, and one patient with fulminating meningococcemia. In an eleventh patient who was untreated, a spinal tap was negative at the time of admission when the fever and rash were maximal. Blood which was drawn for culture at the same time became contaminated. In six of the ten patients who received sulfonamides, in whom lumbar punctures were done at the time positive blood cultures were taken, the absence of even minimal meningeal inflammation was confirmed by repeat punctures done not later than forty-eight hours after admission, and on two patients by punctures done at both twenty-four and

forty-eight hours. In two of these patients sulfonamides were first administered twenty-four hours after the initial lumbar puncture. In our patients with meningitis<sup>14</sup> there was not one who failed to show either meningeal inflammation or a positive spinal fluid culture for meningococci at the first examination. Thus, we have no patient in whom there is evidence that meningitis was induced by a lumbar puncture during a period of bacteremia. This observation is of considerable importance as it tends to confirm the work of Pray,<sup>20</sup> who, working with pneumococci, showed that while it is theoretically possible to infect the meninges in this manner, the likelihood of such an occurrence is extremely remote. Similar results in patients with meningococcemia have been reported by Potter and associates.<sup>19</sup>

The patients in this group are typical of the cases of meningococcemia seen in civilian practice rather than in an army camp. The greatest incidence of the disease is in infants and children. In the majority of cases the disease is mild, at times even evanescent, though the occurrence of meningitis after weeks or even months of illness was a common experience before the use of sulfonamides in treatment.<sup>8</sup> In patients with a mild infection, the diagnosis is very difficult. It usually is suggested by the presence of a skin rash, though this is not always so. The diagnosis can be confirmed most readily by taking blood for culture. This should be done on all patients with a suggestive rash, as well as on all patients with an unexplained fever. By this means only can the diagnosis be established early when the condition is relatively mild. Delay enhances the probability of meningitis which, even in patients with a mild meningococcemia, may be extremely severe.

Severe, fulminating meningococcemia fortunately is rare. Among 296 patients with meningococcic infections, we have encountered only four instances. Meningitis was associated in two of these patients. Three of them have died, all within six hours after admission.

The immune response in patients with meningococcemia is quite similar to that in patients with meningitis. By using the technique of blood serum agglutinations,<sup>18</sup> we have found, in the patients studied, curves of agglutination titers to be quite comparable. In the absence of a positive blood culture, the diagnosis can be established by this procedure (Case 9).

#### SUMMARY

1. Sixteen cases of acute meningococcemia occurring in a general hospital and involving age groups from 2 months to 54 years have been reported. The disease in fourteen patients was characterized by a mild course which cleared up readily with sulfonamide treatment and, in some instances, before sulfonamides were administered. Two patients had severe, fulminating infections which clinically resembled the Waterhouse-Friederichsen syndrome. One of these patients died.

2. Serum agglutinin titers against meningococci were studied in four patients and were found to be present in all of them. The maximum titers obtained were from 1:16 to 1:128.

3. Lumbar puncture during the course of meningococccemia did not result in the development of meningitis in any of the twelve patients on whom it was performed.

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## THE COMPARATIVE EFFECT OF PARENTERAL ADMINISTRATION OF SINGLE MASSIVE DOSES OF VITAMIN D IN AN OIL-ETHER VEHICLE

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**M**ASSIVE doses of vitamin D have been widely used since their first experimental and clinical trial in 1928.<sup>1</sup> The oral route of administration is the most common. Oily solutions of vitamin D have also been intramuscularly injected with satisfactory results. In 1940, one of the authors<sup>2</sup> advocated the parenteral administration of massive doses of vitamin D in an oil-ether vehicle in order to enhance vitamin D absorption.

The speed of absorption of an intramuscularly injected drug depends chiefly on the extent of surface contact between its solvent and the tissues, and the solubility of the drug in the tissues. In the case of an oily solution of vitamin D, both factors are favored by the addition of ether to the oily solvent. Ether materially decreases the viscosity of oil. The alteration of the viscosity follows a hyperbolic curve, i.e., a relatively small proportion of ether reduces the viscosity of oil to a fraction of its original viscosity. As a result, this oil-ether vehicle forms a larger contact surface with the muscle interstices than oil alone, which has been experimentally demonstrated.<sup>2</sup> Moreover, since vitamin D is more soluble in ether than in oil, the ether carries vitamin D to the cell sterols and fats, thus increasing the solubility of the vitamin in the tissues. In this way, vitamin D can be rapidly absorbed while the oil may remain in situ for months.

Clinical observations<sup>2</sup> indicates that the parenteral injection of 600,000 units of calciferol in an oil-ether vehicle cured rickets and tetany at least as promptly as the oral administration of an equal dose of vitamin D; it seemed to be superior to the parenteral injection of vitamin D in oil.

However, an exact evaluation of the comparative efficacy of these three modes of vitamin D administration is lacking. Clinical observations would only reveal differences of a greater magnitude than are to be expected. An exact, comparative evaluation calls for animal experiments with their well-controlled and equal conditions.

The present study attempted such an evaluation by therapeutic and prophylactic experiments on rats.\* Rachitic albino rats and normal weanlings of the same species respectively were used. In both types of experiments the animals were maintained on the *United States Pharmacopoeia* rachitogenic diet No. 2. Both the diet, and distilled water from glass-tipped bottles, were available to the animals ad libitum. The test doses were administered only once,

\*Carried out in the Food Research Laboratories (Dr. B. L. Oser).

and in such dilution that each rat received 1,000 U.S.P. units of pure crystalline vitamin D<sub>2</sub> (calciferol) in 0.1 c.c. of solution. Persic oil was used as solvent for the oral doses, and persic oil, and a mixture of 6 parts of persic oil and 4 parts of U.S.P. ether respectively as solvents for the parenteral administration of vitamin D.

## THERAPEUTIC EXPERIMENTS

Litters of weanling albino rats weighing between 45 and 60 Gm. were distributed into groups of four and fed the rachitogenic diet throughout a depletion period of eighteen to twenty-five days' duration. At the end of the depletion period, roentgenograms were taken of the right knee joint of each animal, and the rats distributed into experimental groups. During the test period the animals were kept in individual, wire-mesh, raised-bottom cages. There were three main groups of thirty animals each, divided according to the method of vitamin D administration, and three subdivisions of each based on the duration of the observation period. Each subgroup consisted of ten rats, five males and five females. The first subgroup for each type of treatment was roentgenographed on the second day and killed on the third to permit estimation of the degree of recalcification by the line test. The second subgroup was roentgenographed on the third and fourth, and sacrificed on the fifth day following dosage. The third subgroup was x-rayed on the third, fourth, and fifth days, and killed on the sixth for line tests. The experimental plan is outlined in the following table:

TABLE I. OUTLINE OF EXPERIMENTAL PLAN OF STUDY ON RATS

GROUP	NO. RATS	1,000 UNITS VITAMIN D <sub>2</sub> DILUTED IN	ROUTE OF ADMINISTRATION	X-RAYED AFTER (DAYS)	TERMINATED FOR LINE TEST AFTER (DAYS)
A	10	Persic oil	Oral	2	3
B	10	Persic oil	Oral	3,4	5
C	10	Persic oil	Oral	3,4,5	6
D	10	Persic oil	Intramuscular	2	3
E	10	Persic oil	Intramuscular	3,4	5
F	10	Persic oil	Intramuscular	3,4,5	6
G	10	Persic oil	Intramuscular	2	3
H	10	and ether	Intramuscular	3,4	5
I	10	(6:4)	Intramuscular	3,4,5	6

The oral dose was administered directly into the stomach by means of a 1 c.c. tuberculin syringe equipped with a No. 18 needle having a ball-tip adaptor to facilitate insertion through the esophagus. The intramuscular dose was injected slowly into the muscles of the right hind leg.

At the beginning of the test period, the tibias of all animals were found to have wide rachitic metaphyses. The appearance of new deposits of calcium in the provisional zone of calcification, the so-called line of healing, was rated in the roentgenographs on an arbitrary scale of 0 to 4, indicating the increasing width of the line.

TABLE II. SUMMARY OF DATA FOR RACHITIC RATS ADMINISTERED A SINGLE DOSE OF 1,000 USP UNITS OF VITAMIN D<sub>2</sub>

GROUP	METHOD OF DOSAGE	AVERAGE BODY WEIGHT (GM.)				AVERAGE DEGREES OF HEALING AS ESTIMATED BY ROENTGENOGRAPH							
		DEPLETION PERIOD		ASSAY PERIOD									
		INITIAL	FINAL		2 DAYS	4 DAYS	5 DAYS	3 DAYS	5 DAYS	6 DAYS			
A	Oral in oil	49.3	68.5	70.3	0.05								
B	Oral in oil	53.3	70.3	74.5	0.75								
C	Oral in oil	51.2	72.0	76.9	0.35								
D	Intramuscular in oil	48.5 <sup>s*</sup>	67.0 <sup>s</sup>	68.1 <sup>s</sup>	0.19 <sup>s</sup>								
E	Intramuscular in oil	50.7 <sup>s</sup>	72.4 <sup>s</sup>	76.0 <sup>s</sup>	0.39 <sup>s</sup>								
F	Intramuscular in oil	50.6	69.7	74.6	0.33								
G	Intramuscular in oil-ether	50.8	75.4	78.1	0.15								
H	Intramuscular in oil-ether	49.8	72.2	75.9	0.15								
I	Intramuscular in oil-ether	51.0 <sup>s</sup>	69.6 <sup>s</sup>	74.1 <sup>s</sup>	0.67 <sup>s</sup>								

\*Superscripts represent number of animals per group; where not indicated, groups consist of ten animals each.

When each of the subgroups was terminated, the tibias were examined by the line test. The degree of healing was rated in accordance with the scale of Bills, Honeywell, Wirick, and Nussmeier.<sup>3</sup>

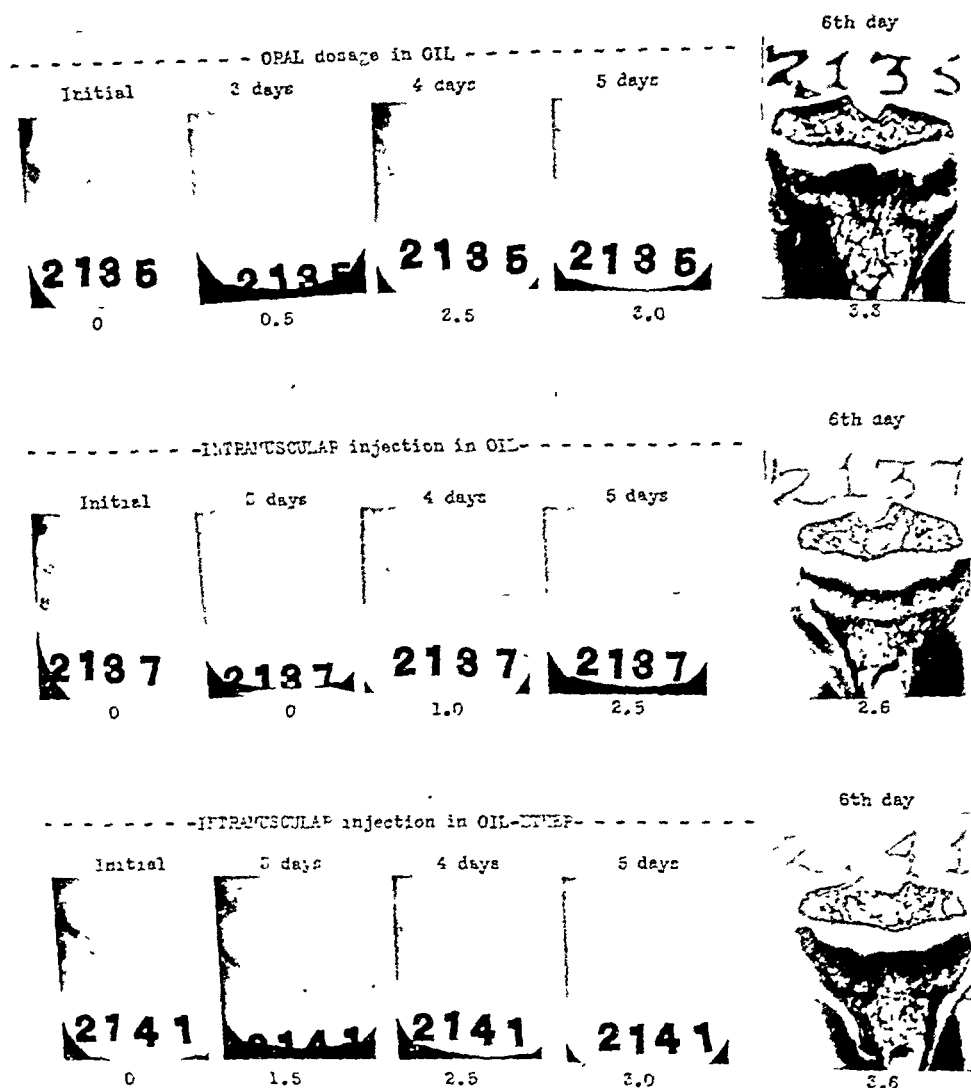


Fig. 1.—Photographs representative of the three treatment groups, showing progress of recalcification of rachitic tibias over a six-day observation period.

Figures below roentgenographs represent degrees of healing (scale 0 to 4).

Figures below microphotographs represent line test ratings (Bills' scale).

Table II contains the results of the therapeutic experiments. Two animals in Group D, and one each in Groups E and I failed to respond to the vitamin D dosage at all, and were omitted from the calculations. A representative series of roentgenograms and magnified microphotographs of tibias of the three groups appears in Fig. 1.

While the roentgenograms are of value in following the course of recalcification in individual animals, the enlarged microphotographs of the tibias show more clearly the difference in the effects of the three methods of vitamin D administration. The evaluations have therefore been based on the line test data. These have been subjected to statistical analysis, and the average responses, their standard errors, and the significance of the differences between the averages appear in Table III. For the size of the groups used in these experiments a *t*-value of 2.1 or more indicates significance in the differences between any two averages.

TABLE III. SUMMARY OF STATISTICAL DATA FOR THERAPEUTIC TESTS

GROUP	METHOD OF DOSAGE	DURATION OF TEST (DAYS)	DEGREES OF HEALING† (LINE TEST RATINGS)		SIGNIFICANCE OF DIFFERENCE‡	
			AVERAGE	STANDARD ERROR	GROUPS COMPARED	T-VALUE
A	OO	3	2.04	±0.067	A and D	0
D	IMO	3	2.04 <sup>s</sup>	±0.080	D and G	0.3
G	IMOE	3	2.01	±0.122	G and A	0.3
B	OO	5	2.94	±0.176	B and E	1.2
E	IMO	5	2.62 <sup>9</sup>	±0.205	E and H	1.0
H	IMOE	5	2.79	±0.159	H and B	0.5
C	OO	6	3.13	±0.128	C and F	3.4
F	IMO	6	2.57	±0.109	F and I	4.0
I	IMOE	6	3.32 <sup>9</sup>	±0.122	I and C	1.1

\*OO, Oral, in oil medium; IMO, intramuscular in oil medium; IMOE, intramuscular in oil-ether medium.

†Superscripts indicate the number of observations used in calculating the averages. Those omitted were completely negative responses.

‡For groups of this size, a *t*-value of 2.1 indicates a significant difference.

Table III shows that differences in the effect of the three methods of treatment are not significant three and five days after the administration of vitamin D. However, by the sixth day, when recalcification is well advanced, the superiority of the intramuscular injection of vitamin D in oil-ether solution as well as of the oral administration of vitamin D in oil over the intramuscular administration in oil is statistically significant, as indicated by *t*-values of 3.4 and 4.0 respectively. The intramuscular injection of vitamin D in oil-ether was somewhat more effective than the oral administration of vitamin D in oil.

#### PROPHYLACTIC EXPERIMENTS

The experimental conditions were similar to those of the therapeutic experiments. However, the prophylactic doses of vitamin D were administered immediately after weaning, when the feeding of the rachitogenic diet was started. The observation period was three months.

A single dose of 1,000 units of calciferol was given to each animal by the routes described in the therapeutic experiments. Three groups of thirty animals each received the prophylactic doses orally in oil, intramuscularly in oil, and intramuscularly in oil-ether respectively. Each of these groups was divided

into three subgroups of ten rats which were killed for histologic examination of the bones after thirty, sixty, and ninety days respectively. After each of these intervals, all survivors were x-rayed to see whether any decalcification had taken place.

A summary of the observations appears in Table IV. Representative series of photographs demonstrating the progressive condition of a typical animal receiving each form of prophylaxis are shown in Fig. 2. The interpretation of the roentgenographs is based on a rating of the width of the metaphyses, using an arbitrary scale of 0 to 4 to indicate increasing degrees of decalcifica-

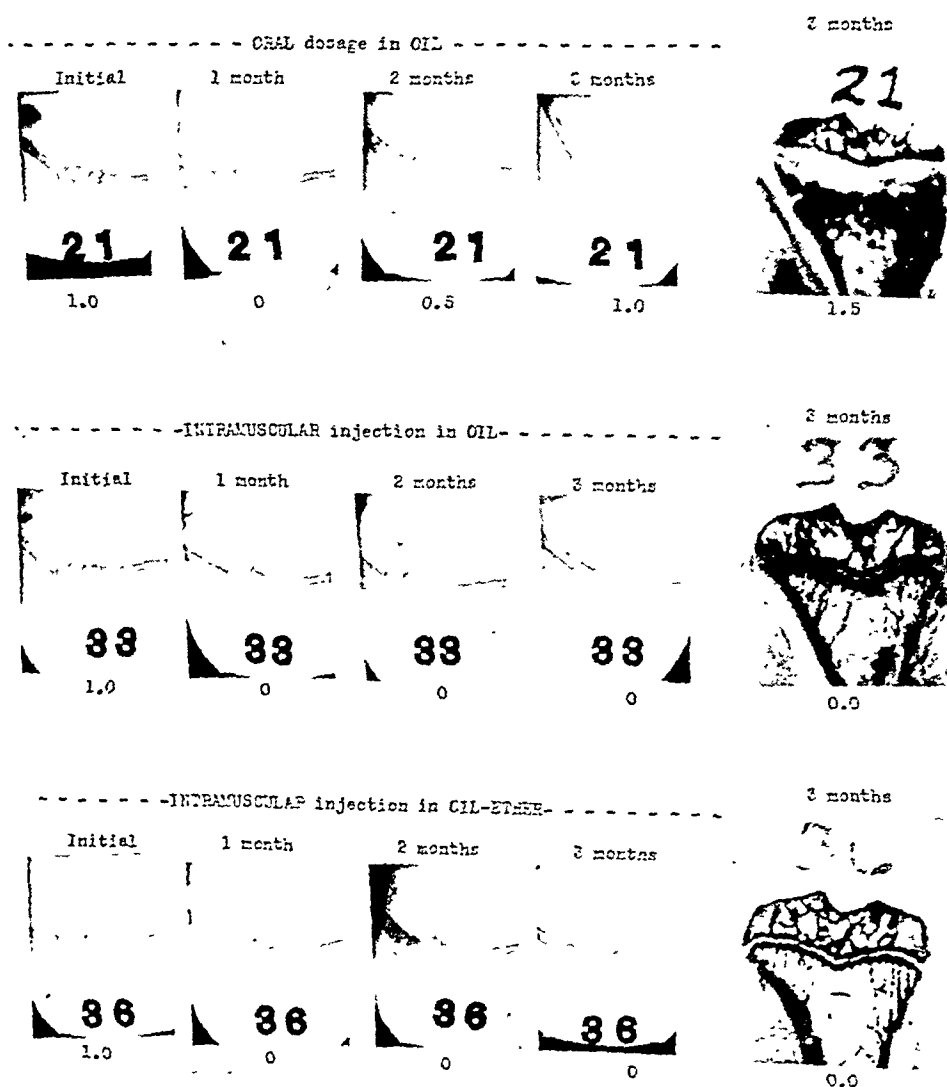


Fig. 2.—Photographs representative of the three treatment groups, showing development of metaphysis over a three-month period.  
Figures below roentgenographs and microphotographs represent ratings for metaphysis widths (scale 0 to 4).

TABLE IV. SUMMARY OF DATA FOR RATS ADMINISTERED A SINGLE PROPHYLACTIC DOSE OF VITAMIN D<sub>2</sub>

GROUP	METHOD OF DOSAGE	AVERAGE BODY WEIGHTS (GM.)				AVERAGE WIDTH OF METAPHYSIS AS ESTIMATED BY											
						ROENTGENOGRAPH						HISTOLOGIC TEST					
		0 MONTHS	1 MONTHS	2 MONTHS	3 MONTHS	0 MONTHS	1 MONTHS	2 MONTHS	3 MONTHS	1 MONTHS	2 MONTHS	3 MONTHS	1 MONTHS	2 MONTHS	3 MONTHS		
J	Oil, oral	48.0	75.8			0.53	0.51					0.60					
K	Oil, oral	48.1 <sup>a</sup> *	78.2 <sup>a</sup>	121.9 <sup>a</sup>		1.13 <sup>a</sup>	0.28 <sup>a</sup>	0.94 <sup>a</sup>									
L	Oil, oral	47.9	74.9	116.2	151.3	1.0	0.22	0.50	0.70					0.85 <sup>a</sup>			0.72
M	Oil, intramuscular	47.4	73.2			1.05	0.11					0.40					
N	Oil, intramuscular	47.4	80.3	120.1		1.09	0.23	0.13					0.07				
O	Oil, intramuscular	47.8	80.6	123.5	157.0	1.08	0.17	0.06	0.02						0.10		
P	Oil-ether, intramuscular	47.8	79.4			0.95	0.48					0.56					
Q	Oil-ether, intramuscular	48.6	84.5	129.5		0.83	0.29	0.17					0.02				
R	Oil-ether, intramuscular	47.9	74.2	116.5	153.0	1.18	0.30	0.09	0.01							0.0	

\*Superscripts indicate number of animals per group. One rat in this group died and was omitted from the calculations.

tion. The stained tibias were rated in terms of decalcification of the metaphyses, in contrast to the therapeutic experiments where degrees of recalcification were used for interpretation. The roentgenographs demonstrate the condition of the animals during the course of the experimental period, but the magnified microphotographs show more clearly than the x-rays the difference between the prophylactic effect of the three methods. The initial readings for metaphyseal width in the weanling rats, averaging approximately one, do not express the degree of rickets but rather indicate the normal cartilagenous character of the undeveloped infantile bones. During normal development this cartilagenous zone diminishes as calcification proceeds.

All three methods of administering single massive doses of vitamin D proved to have a prolonged protective effect. At the end of the first month the metaphyseal widths decreased normally in all groups. In the groups receiving the parenteral doses the bones continued to calcify normally throughout the entire three-month period. However, in the group receiving oral doses in oil, no further decrease but rather a slight, progressive increase in the average width of the metaphyses was observed after the second and third month. The incidence of this decalcification, though quantitatively small, was sufficient to give it significance.

A statistical analysis of the data derived from the microphotographs is presented in Table V. It shows that after one month the width of the metaphyses diminished to about the same degree in all groups. After two and three months, however, differences became apparent. The prophylactic effect of parenterally administered vitamin D doses proved to be superior to that of oral doses. The statistical significance of these differences is expressed by t-values of 3.3 and 3.7 after two months, and of 2.1 and 2.6 after three months, when the animals receiving vitamin D in oil by mouth were compared with the groups receiving parenteral vitamin D doses in oil and in oil-ether solution.

TABLE V. SUMMARY OF STATISTICAL DATA FOR PROPHYLACTIC TESTS

GROUP	METHOD OF DOSAGE*	DURATION OF TEST (DAYS)	RATINGS OF METAPHYSIS WIDTHS		SIGNIFICANCE OF DIFFERENCE†	
			AVERAGE	STANDARD ERROR	GROUPS COMPARED	T-VALUE
J	OO	30	0.60	$\pm 0.120$	J and M	1.2
M	IMO	30	0.40	$\pm 0.106$	M and P	1.0
P	IMOE	30	0.56	$\pm 0.111$	P and J	0.2
K	OO	60	0.82	$\pm 0.217$	K and N	3.3
N	IMO	60	0.07	$\pm 0.034$	N and Q	1.4
Q	IMOE	60	0.02	$\pm 0.013$	Q and K	3.7
L	OO	90	0.73	$\pm 0.280$	L and O	2.1
O	IMO	90	0.10	$\pm 0.10$	O and R	1.0
R	IMOE	90	0.0	$\pm 0.0$	R and L	2.6

\*OO, oral, in oil medium; IMO, intramuscular in oil medium; IMOE, intramuscular in oil-ether medium.

†For groups of this size a t-value of 2.1 indicates a significant difference.



## SUMMARY AND CONCLUSIONS

Experiments on rats were carried out to determine the comparative therapeutic and prophylactic effect of a single massive dose of vitamin D<sub>2</sub> administered orally in oil, intramuscularly in oil, and intramuscularly in oil-ether solution. All animals were followed by x-ray, and examined by the line test. The line test data were submitted to statistical analysis.

Six days following the administration of 1,000 units of vitamin D<sub>2</sub> to rachitic rats, the average degree of line test healing was 3.32 with the intramuscular oil-ether injection, 3.13 with the oral administration in oil, but only 2.57 with the intramuscular injection in oil. The superiority of the oil-ether injection and the oral dose over the parenteral administration in oily solution was statistically significant.

The protective effect of a single dose of 1,000 units of vitamin D<sub>2</sub> showed differences between the three methods only after two and three months. Three months following the administration of the prophylactic doses, the average degree of decalcification was 0.0 with the oil-ether injection, 0.1 with the oil injection, and 0.72 with the oral doses in oil. The superiority of the oil-ether injection and the oil injection over the oral doses was statistically significant.

The superiority of the parenteral vitamin D<sub>2</sub> administration in an oil-ether vehicle in the therapeutic as well as the prophylactic experiments seems to indicate quick absorption and satisfactory retention of the vitamin administered by this method.

The inferiority of the parenteral administration of vitamin D<sub>2</sub> in oil in the therapeutic experiments may be ascribed to a delayed vitamin D absorption from the oily deposit in the tissues.

The inferiority of the oral administration of vitamin D<sub>2</sub> in oil in the prophylactic experiments may be explained by incomplete absorption of massive doses from the gastrointestinal tract and loss of vitamin D with the feces.

If observations in animals are applicable to infants and children, one may expect that intramuscular injection of a single massive dose of vitamin D<sub>2</sub> in an oil-ether vehicle cures rickets at least as promptly as other methods of administration, and is at least equivalent to the other methods in its prophylactic effect, giving complete protection against rickets for at least three months. Impressions gained from clinical experience<sup>2</sup> are in conformity with these deductions.

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## CAPILLARY FRAGILITY AND MENSES IN RHEUMATIC GIRLS

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THIS paper discusses the duration and frequency of menses in twenty-eight ambulant rheumatic girls, and records capillary resistance in various phases of their menstrual cycle. We are unable to locate a similar study.

Capillary resistance was determined with a modified Dalldorf resistometer, as previously described.<sup>1</sup> Capillary resistance is the minimal amount of suction (centimeters of mercury negative pressure) applied for one minute to the skin of the forearm just below the antecubital space, which produces one petechia or more. Normal values are dependent on many factors, including season and age. At age 13.4 years, the average for this group, capillary resistance in non-rheumatic children is about 27 cm., and in rheumatic children, 17.4 cm.<sup>1, 2</sup> When values of 10 cm. are obtained, capillary resistance is distinctly abnormal, and at 5 cm., capillary fragility is extreme.

Several diseases produce capillary fragility and excessive menstrual flow, sometimes hastening the appearance of menses. In scarlet fever, streptococcus toxin causes low capillary resistance<sup>1, 3</sup> and menorrhagia.<sup>4</sup> Measles is attended with extreme capillary fragility<sup>5</sup> and menses in the presence of an attack may occur early and be more severe.<sup>4</sup> Pneumonia produces low capillary resistance<sup>6</sup> and at times an excessive menstrual flow.<sup>7</sup> If infection develops immediately after menstruation, recurrence of the bleeding may occasionally occur.<sup>4</sup>

In rheumatic patients there is evidence of increased capillary permeability<sup>2, 8, 9</sup> and hemorrhagic phenomena.<sup>9</sup>

In normal subjects the age of menarche, duration of menses, and length of menstrual cycle may be quite variable. The peak age of menarche is observed at 13 years.<sup>10, 11, 13, 14</sup> In one series of 10,000 cases it was 13.9 years.<sup>15</sup> Puberty tends to be delayed in northern Europe (Scandinavia) while in Italy and Greece it may commence as early as ages 10 to 12.<sup>16</sup>

The duration of menses is usually three to five days,<sup>12, 17</sup> but both lesser and greater periods of menstrual flow occur in healthy girls. The length of the menstrual cycle was determined by Arey<sup>15</sup> in about 1,500 women and girls, including some 20,000 calendar records. The commonest length of 8,462 cycles (furnished by 585 persons) is twenty-eight days both for puberal girls and for adult women. The average length of all cycles is 33.9 days for girls and 29.5 days for women.

In this study, to determine variations in capillary resistance, the menstrual cycle was divided into three stages: (1) premenstrual, from the fourth day preceding menses to and including the first and second day of menses, (2)

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menstrual, from the third day to the end of menses and (3) intermenstrual, from the end of menses to the fourth day prior to next menses. The premenstrual stage arbitrarily included the first two days of menses since it has been shown that capillary resistance in normal healthy female subjects is lowest during the few days prior to and on the first and second days of menstruation.<sup>19, 20</sup> Capillary resistance readings in twenty-eight rheumatic girls may be noted in Table I.

TABLE I. MENSTRUAL DATA IN TWENTY-EIGHT RHEUMATIC GIRLS

PATIENT	AGE	AGE AT MEN- ARCHÉ	DURATION OF MENSES (DAYS)	MEN- STRUAL CYCLE (DAYS)	CAPILLARY RESISTANCE (CM. OF HG SUCTION)					
					PRE- MENSTRUAL* AVERAGE	MENSTRUAL* AVERAGE	INTER- MENSTRUAL AVERAGE			
S. C.	15		5-6	21-28	20	20	(15,25)	20		
V. W.	15	13	3-5	24-30	(15,25)	20	25	(15,15)	15	
N. D.	13	13	5	28		15	—	(20,30)	25	
H. T.	13	12	6-7	28-42		5	10		20	
N. B.	13	12	6-7	28		—	—	(15,15)	15	
J. G.	13	11½	4-5	21-30		—	15	(15,20)	17½	
Y. W.	14	—	4-6	30		20	—		15	
K. S.	11	11	4-5	—		15	10		25	
H. W.	15	—	5-6	21-28	(25,10)	17½	10		15	
E. F.	14	—	4	—		—	—		15	
C. M.	16	13	4	26-28		10	—		10	
B. W.	14	14	7	28	(10,10)	10	—	(20,15,10)	15	
R. G.	11	10½	3-7	21-28		—	—		15	
B. I.	13	12	4	28		—	15		15	
L. L.	14	—	4-14	28		—	10		15	
V. M.	14	—	5	—		15	25	(20,25,15)	20	
T. M.	13	—	5-8	21		10	15		20	
R. D.	13	12½	5	26-28		15	—		20	
L. S.	12	12	5	—		—	—		15	
M. P.	13	12	3-4	28		25	—		25	
I. J.	13	—	5	—		—	—	(15,15)	15	
L. C.	14	—	3-7	14-28		10	—	(10,15,20)	15	
V. G.	12	10	3-4	30		—	(20,15)	17½	(15,20)	17½
R. D.	11	11	4-6	28		5	(5,5)	5	(5,5,15)	8
F. A.	16	—	4-5	—		10	—		20	
E. G.	11	10	5	28-30		—	—		(20,15,5)	13
E. P.	15	13	4	26		—	—		(10,20)	15
A. A.	15	—	4-7	21-28	(10,10)	10	10	(5,15,15)	12	
Average	13.4	11.9	5.1	26.9		13.7	14.4		16.7	

\*As defined in text.

#### SUMMARY AND DISCUSSION

*Age of Menarche.*—The onset of menses tended to be early in this group of rheumatic girls, records being available in only seventeen cases. Three girls started to menstruate at age 10. The average age of menarche was 11.9 years, in contrast to 13½ years, the average age for American girls.<sup>14</sup>

*Length of Menses.*—This averaged 5.1 days in twenty-eight rheumatic girls, several having periods lasting seven days or longer. In nonrheumatic girls, the average duration is closer to four days.

*Menstrual Cycle.*—The interval between menstrual periods averaged 26.9 days, as compared with 33.9 days for nonrheumatic girls.<sup>15</sup>

*Capillary Resistance.*—The average capillary resistance during the four days prior to menses and the first two days of menses was 13.9 cm. It rose

slightly to 14.4 cm. during the remainder of menses. In the intermenstrual period capillary resistance was 16.7 cm., a rise of 3.0 cm. over the premenstrual phase. It is generally accepted that some glandular influence, probably ovarian, is responsible for lowered capillary resistance and general tissue congestion in the premenstrual phase. However, this glandular influence on capillary resistance is not so great as that produced by a seasonal influence, which is worthy of comment.

The seasonal influence on capillary resistance was noted by Roberts and her co-workers<sup>21</sup> in eighty-five institution children. These workers found that capillary resistance was 23 cm. in August and 16.5 cm. in April. In rheumatic children we<sup>2</sup> noted an even greater seasonal variation, capillary resistance being 23.3 cm. in September and 14.2 cm. in February and March, a difference of 9.1 cm. We stated our belief that streptococcus toxin may be important in accounting for these seasonal variations.<sup>1, 2</sup>

It was formerly held that vitamin C deficiency might explain seasonal variations in capillary resistance noted in large groups. Two factors, however, rule out the influence of this vitamin. The first is the failure of thirteen groups of workers either to improve capillary resistance by administering vitamin C or to find any definite relationship between blood ascorbic acid values and capillary resistance.<sup>1</sup> The second weakness in the vitamin theory is that it does not explain the sudden drop in capillary resistance noted in the fall.<sup>1, 21</sup>

The sudden increase in capillary fragility noted in the fall is probably caused by increased amounts of streptococcal toxins in the blood following the first chilling weather.<sup>1</sup>

Seasonal variation in capillary resistance may be the effect of streptococcal toxin in both rheumatic and nonrheumatic individuals. The streptococcus is uniformly present in all pharynges.<sup>1</sup> Streptococcic activity is minimal at the end of summer and capillary resistance is highest at this time.. Following the first chilling weather in the fall, there is a mass onset of streptococcic colds,<sup>22</sup> and many symptoms appear which might be caused by the streptococcus such as sniffing, hacking, muscular aches, sinusitis, and rheumatic fever. There is a coincidental sudden drop in capillary resistance. However, the peak of streptococcic and rheumatic activity is reached in the spring when capillary resistance is lowest.

In summary, then, it may be stated that while the glandular influence on capillary resistance seen in the menstrual cycle is considerable (3.0 cm.), it is of lesser magnitude than the influence of various infections, such as streptococcus infections, rheumatic fever, scarlet fever, pneumonia, and measles. These infections not only lower capillary resistance greatly but may precipitate menses and produce menorrhagia.<sup>4, 7, 23</sup>

#### CONCLUSIONS

1. Bleeding phenomena in rheumatic girls are evidenced by an early menarche, prolongation of menses and shortening of the menstrual cycle.
2. The bleeding tendency is increased during the premenstrual and menstrual phase, at which time there is a diminished capillary resistance amounting

to 3 cm. of mercury suction. This capillary fragility is presumably under glandular control.

3. An even greater influence in producing the capillary fragility and menorrhagia of rheumatic girls is exerted by rheumatic toxin.

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## Case Reports

### MENINGITIS DUE TO *SALMONELLA* MANHATTAN

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**M**ENINGITIS caused by a *Salmonella* organism has been reported in ninety-three instances. The mortality rate in the reported cases has been high. Among the drugs used, sulfonamides have been the most effective. Sulfaguanidine is effective against *Salmonella paratyphi* A and *Salmonella choleraesuis* but ineffective against other organisms of the *Salmonella* group.<sup>1</sup> Sulfanilamide, sulfathiazole, and sulfadiazine have been used.

The following report is of a one-month-old infant who had enteritis and meningitis caused by *Salmonella manhattan* and who recovered following the use of streptomycin.

This female infant was seen July 6, 1946. At that time a history of having had a slight persistent diarrhea since the fourth day following delivery was noted. She was sent home from the hospital nursery on the eighth day of life. She was breast fed with a complementary evaporated milk formula. The infant was irritable, and had diarrhea. At the age of 17 days, a physician changed the formula to homogenized milk, but the diarrhea persisted. It was not until two days prior to admission to Milwaukee Children's Hospital at the age of one month that the diarrhea became severe, and the infant passed ten to twelve green, watery stools daily.

The past history was as follows: the health of the mother during her prenatal period was excellent; Wassermann test was negative; and delivery was made by low forceps. Although alleged to be three weeks premature, the child weighed 6 pounds, 8 ounces at birth and was perfectly healthy. She was the fifth sibling. The family history was essentially negative for important hereditary diseases and also negative for infectious diseases during the mother's prenatal period.

Physical examination on admission to Milwaukee Children's Hospital revealed a critically ill female infant one month of age, with a subnormal temperature and a tense anterior fontanel. Nystagmus was present and the child was slightly hypertonic. The pharynx was mildly injected. A spinal puncture was performed immediately. The fluid obtained was under moderately increased pressure, turbid, and opalescent. Further examination revealed 3,080 cells per cubic centimeter, a 4 plus Pandy, and 9 mg. per cent sugar. A gram-negative organism was found and tentatively identified by smear as *Hemophilus influenzae*. Immediate therapy consisted of intravenous 5 per cent glucose in normal saline to restore hydration and 22.5 grains of subcutaneous sulfadiazine. This initial amount was followed by 3.3 grains every four hours (approximately 2½ to 3 grains per pound of body weight daily). Because of the tentative identification of the organism as *H. influenzae type B*, 100 mg. of Alexander's anti-influenzal serum was given intravenously. No further serum therapy was given because the laboratory later identified the organism by culture as not *H. influenzae type B*, but as *Bacillus paratyphosus*. Because of the conflicting

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laboratory reports, the organism was sent to Dr. P. R. Edwards of the National Salmonella Center, Agricultural Experiment Station, Lexington, Ky.<sup>2</sup> Doctor Edwards identified the organism as *S. manhattan* (V1, V111, d, 1, 5). The identifying characteristics of this motile, gram-negative organism were as follows: lactose, negative; saccharose, negative; dextrin, negative; dextrose, acid and gas; mannite, acid and gas; maltose, acid and gas; xylose, acid and gas; dulcitol, acid and gas; salicin, negative; sucrose, negative; H<sub>2</sub>S, positive; indol, negative; gelatin, not liquefied; lead acetate, blackened in eighteen hours; litmus milk, acid.

Streptomycin was given intramuscularly, 25,000 µg per pound body weight daily in divided doses every three hours, and intrathecally 25,000 micrograms once daily, as recommended by Dr. Chester Keefer of the National Research Council, Committee on Chemotherapeutics. Sulfadiazine therapy was continued until the organism was identified temporarily as one of the *Salmonella* group (fifth hospital day). The amount of sulfadiazine given was approximately 2.5 grains per pound body weight daily. During these five days of hospitalization the patient continued to become more spastic and developed difficulty in swallowing. At the time sulfadiazine was discontinued, the cultures of both the stool and spinal fluid showed the pathogen still present (Table I). The child was

TABLE I. SUMMARY OF SPINAL AND CISTERNAL FLUID FINDINGS

DATE	7/6	7/8	7/9	7/15	7/16	7/19	7/24	8/9	8/23
No. cells	3,080	3,480	1,300	65	109	177	212	26	12
Sugar (mg. %)	9	25	29	33	49	32	33	48	47
Culture	pos.	—	pos.	neg.	—	neg.	neg.	—	—
Pandy	+++	++	+++	++	++	++	++	+	tr.

having momentary twitchings and convulsions, and the spinal fluid was becoming more difficult to obtain from the lumbar level. Heparin was not given intrathecally as advised by Alexander,<sup>3</sup> but small amounts of air were injected intrathecally in the hope that a complete block would not occur. A block, however, did occur, and cisternal taps had to be resorted to for the intrathecal injections of the streptomycin. The condition of the child on the sixth day was very poor. She was convulsing continuously, even with phenobarbital sedation.

On the tenth hospital day, 60 c.c. of blood were given intravenously and it was noted that from that day on the fever became of a low-grade type.

On the tenth day of streptomycin therapy, a rash was noted, particularly over both lower extremities and on the chest. Most of the lesions were erythematous, some were of the roseolar type, and some were persistent, large wheals of the angioneurotic edema type. There was marked dermatographism. This eruption rapidly disappeared on cessation of streptomycin administration on the fourteenth hospital day. The dermatographism, however, persisted for a longer time. The rash was considered to be due to a streptomycin toxic manifestation rather than one produced by meningitis.

The spinal fluid became negative for organisms on the sixth hospital day (four days after streptomycin was begun), and the stool cultures were negative on the fourteenth day. The spinal fluid was again obtained by lumbar puncture on the thirty-fifth hospital day, and it was assumed that the spinal fluid block was released spontaneously. Blood culture was never positive for organisms. It is regrettable that a blood culture was not taken until after the spinal fluid became negative. At no time was a positive agglutination reaction obtained with the child's serum, as expected, because a child this age does not readily manufacture antibodies. On discharge (the fiftieth hospital day) the child appeared in good general health (having gained one pound, 14 ounces since admission):

the neck was not stiff; the pupils were equal and reacted to light; no ptosis or nystagmus was present; and there was no facial palsy. Two weeks after discharge the child was rechecked in the clinic and at that time no abnormal neurologic findings were present.

In the hope of ascertaining the source of the infection, epidemiologic studies were begun by the Milwaukee City Health Department. All contacts of the child in the home and in the hospital where the child was born were examined. This included father, mother, grandparents, doctors, nurses, and nursery aides. Urine and stool cultures were obtained from everyone known to have been or suspected of having been in contact with the child or its food. Blood agglutinations were done on the immediate family. No evidence of carriers was found.

#### SUMMARY

1. The case of a patient with *S. manhattan* meningitis is reported. This is the first case of *S. manhattan* meningitis reported in the literature.
2. Recovery without sequelae followed treatment of the case with streptomycin.
3. Because of a block of the spinal fluid, the cisternal route of administration had to be used.

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## HYPERTROPHIC PULMONARY OSTEOARTHROPATHY

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IT IS well established that among adults the condition known as hypertrophic pulmonary osteoarthropathy (Pierre-Marie-Bamberger's Disease), found in long-standing pulmonary or cardiac disease, is not uncommon. However, most authorities agree that the condition is rare in children. Caffey<sup>3</sup> states that in twenty years at Babies' Hospital no cases have come to his attention. That the condition does occur more often in children than is suspected is noted by Kennedy, who describes a case in a 7½-month-old infant with multiple lung abscesses and bronchopneumonia.

A few instances of this condition and its rarity have also been noted by others. E. Miller<sup>16</sup> reports a case of a 14-year-old boy with reticulum cell sarcoma of the thymus. Kline reports another case in a 14-year-old boy with tuberculosis of the knee, spine, and lungs. D. M. J. Miller<sup>15</sup> reports still another case in an 8-year-old child with pneumonia and purulent bronchitis. He also quotes Whitman, Davis, Thorburn, and Gillet as having seen cases of hypertrophic pulmonary osteoarthropathy in children.

### ETIOLOGY

The underlying causes are many, but the primary precipitating etiologic agent of this condition is still unknown. Hypertrophic pulmonary osteoarthropathy, as the name implies, is most often associated with, and secondary to chronic pulmonary infections, usually lung abscess, bronchiectasis, bronchial asthma of long standing, chronic bronchitis, and late carcinoma of the lung. Pulmonary tuberculosis is one of the few chronic conditions of the lung in which this bony alteration is very infrequently found. However, Kessel<sup>11</sup> reports that among 100 patients with advanced pulmonary tuberculosis there were some manifestations of hypertrophic pulmonary osteoarthropathy in certain cases.

The second underlying cause is chronic heart disease, especially the congenital type. The condition is also ascribed to other causes of lesser importance, i.e., chronic diseases of the liver and intestinal tract, polycythemia vera, hypothyroidism, thymic tumors, and other mediastinal growths. Dyspituitarism has also been considered one of the causes.

Hypertrophic pulmonary osteoarthropathy of idiopathic type and unknown etiology in families has also been described by Freund,<sup>5</sup> Campbell, and Sacosa.<sup>4</sup>

In reference to the primary etiologic agent for this disease, Mendlowitz and Leslie<sup>14</sup> have been able to reproduce this pathologic entity experimentally in a dog by the anastomosis of the left auricle to the left pulmonary artery. This resulted in an increase of cardiac output. It was concluded that the bony changes produced may have been due to the constantly excessive peripheral blood volume increasing periosteal nutrition and thus stimulating bone proliferation.

Other investigators, such as Funk<sup>7</sup> and Kessel,<sup>11</sup> ascribe the alterations of the periosteum to toxins or venous stasis.

### PATHOLOGY AND CLINICAL FINDINGS

The cortical bone may become thin while the periosteal tissue will thicken occasionally to as much as 6 to 8 mm. Eventually hyalinization will take place

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and finally ossification of the periosteum, whose external surface may merge with the skeletal muscle. This ossified periosteum, having an irregular contour, may become indistinguishable from the underlying cortical bone.

The rapidity of development of these bony changes varies considerably. In some cases, periostitis develops within a few months after the initial pulmonary disease. In others, the bony alterations may not develop until many years. The changes usually involve the distal thirds of the long bones, and may affect the ulna, radius, tibia, and fibula. To a lesser extent the humerus, femur, carpals, metacarpals, and proximal phalanges may be involved. The process later extends proximally, and may involve the entire bone.

The early joint changes are confined largely to the periarticular tissues. In the later stages, erosion of the cartilage, lipping at the articular edges, and even a moderate degree of ankylosis may develop. Pain may accompany the periostitis and these arthritic changes.

Clubbing of the fingers and/or toes is always found associated with hypertrophic pulmonary osteoarthropathy; it merely represents the first stage in this disease. The phenomenon of clubbing is due to soft tissue swelling and usually is not associated with thickening of the terminal tufts or overlying periostitis.

Both the periostitis and the clubbing may diminish in severity and become less marked in proportion to the improvement of the suppurative pulmonary condition. They may even disappear entirely, only to recur with the exacerbation of the pulmonary disease. However, the condition is not always a reversible one, and the bony changes may remain permanently, even though the patient may be clinically cured.

Some authors report peculiar facial alterations associated with this condition. This consists of a thickening of the subcutaneous tissues about the nose and malar prominences, so that the nose and facies assume a globular appearance. Prognathism may be observed, but it is not as marked as in acromegaly.

#### CASE HISTORY

The patient is a 2-year-old white female, admitted to New York City Hospital on April 1, 1946. Her chief symptoms were chronic cough of four months' duration, considerable weight loss, and anorexia. The cough was not productive.

*Present Illness.*—Since January, 1946, when the patient developed a "cold" not responding to therapy, she was ill with cough, dyspnea, and loss of about 15 lbs. The child had a normal birth; her diet was adequate. Five older siblings are all living and well. The mother is in good health; the father died, cause unknown. There have been no previous illnesses and no familial history of tuberculosis or any other contact infection.

*Physical Examination.*—The patient appeared chronically ill and emaciated, with drawn facies. Temperature was 99° F.; pulse, 120 per minute; respiration rate, 40 per minute.

Findings were essentially negative except as noted below.

*Head and Neck.*—Moderate posterior cervical adenopathy, not tender.

*Chest.*—Movements were restricted during respiration, especially on the right side.

Heart was normal, except for tachycardia.

Lungs showed tactile fremitus, diminished on the right side anteriorly and posteriorly, and there was dullness to percussion in the same regions. The breath sounds were tubular in quality and bronchophony was present over the upper third of the right chest. Breath sounds were diminished over the lower half of right chest, posteriorly. There were coarse moist râles scattered throughout both left and right sides, posteriorly.

*Extremities.*—Marked clubbing of the distal ends of all fingers and toes was present.

*Course.*—On the day of admission a roentgenogram of the chest (Fig. 1) showed that the right lung was collapsed and a hydropneumothorax was present, the fluid level being at the fourth interspace anteriorly. A thoracentesis was performed the following day, but only a few drops of turbid, blood-tinged material were obtained. Smear of this fluid showed a considerable number of pus cells, but was negative for any bacterial pathogens. The patient was given multiple small blood transfusions and placed on penicillin therapy (20,000 units every three hours). Temperature course was very irregular, at times reaching 101° F., and the patient showed no significant response to penicillin therapy. This therapy was given in long repeated courses throughout the period of illness. On April 29 the patient's cough became productive of a small amount of cream-colored sputum. Repeated roentgenograms of the chest showed slight diminution in the amount of fluid at the right base. Otherwise, the findings were unchanged.



Fig. 1.—Roentgenogram of chest on day of admission shows collapse of the right lung and fluid level at fourth anterior interspace. Heart and mediastinal contents are displaced slightly to the right.

Bronchoscopy on May 2 showed a large amount of mucopurulent material present in the right main bronchus. The pus had no foul odor. A bronchogram showed no evidence of bronchopleural fistula at this time.

On June 7 a thoracotomy was performed by partial resection of the eighth rib. Considerable pus was drained and thereafter the child began to show slow but definite clinical improvement. The temperature still rose to 101° F. at times. Clubbing of fingers persisted in the same severity. Roentgenogram of long bones taken July 3, 1946, showed considerable thickening and periosteal proliferation in the femur, tibia and fibula, radius, and ulna bilaterally, including the distal half of both humeri. Repeated radiographic study of long

bones on July 25 showed no change in this periosteal proliferation (Figs. 2 and 3). A diagnosis of hypertrophic pulmonary osteoarthropathy was made secondary to the chronic empyema.

The subsequent course of illness was essentially unchanged, except for development of a bronchopleural fistula. On September 5, temperature rose to 104° F. and did not fall. More extensive rib resection was performed by partial removal of the fifth to ninth ribs on the right side. Very little drainage was obtained. The temperature fell somewhat, and the child showed some clinical improvement. Roentgenogram of the chest at this time showed slight re-expansion of the right upper lobe; less fluid was present at the right base than on previous examination. Otherwise, findings were essentially unchanged.



Fig. 2 - Roentgenogram of the upper extremities taken July 3, 1946, shows marked thickening of the periosteum along the shafts of the radius, ulna, and distal half of the

Blood counts during the course of the disease showed a relative and absolute lymphocytosis. This was attributed to the chronicity of the illness.

Bone marrow puncture performed Sept. 15, 1946, showed a relatively high proportion of cells of the lymphocytic series in the mature stage, with a tendency toward hypoplasia of both the myeloid and lymphocytic series. These findings were not consistent with that of the lymphoblastomas or leucemia.

Repeated smears and cultures throughout the course of the illness taken from sputa, bronchoscopy, and from several thoracotomy procedures were negative for tubercle bacilli. Guinea pig inoculations were also negative. At times cryptococci were found in some cultures; *Staphylococcus aureus* and Gram-positive rods and *Bacillus pyocyaneus* were also found. On July 8, and throughout the course of the illness after this date nonspecific yeastlike fungi were found. These increased in amount as the illness progressed.

Many courses of penicillin therapy were instituted, including local irrigation into the pleural cavity. Sulfadiazine was also given in adequate doses for some time. However, during all the time described, remissions were only to be followed by exacerbations. The latter were of decreasing severity.

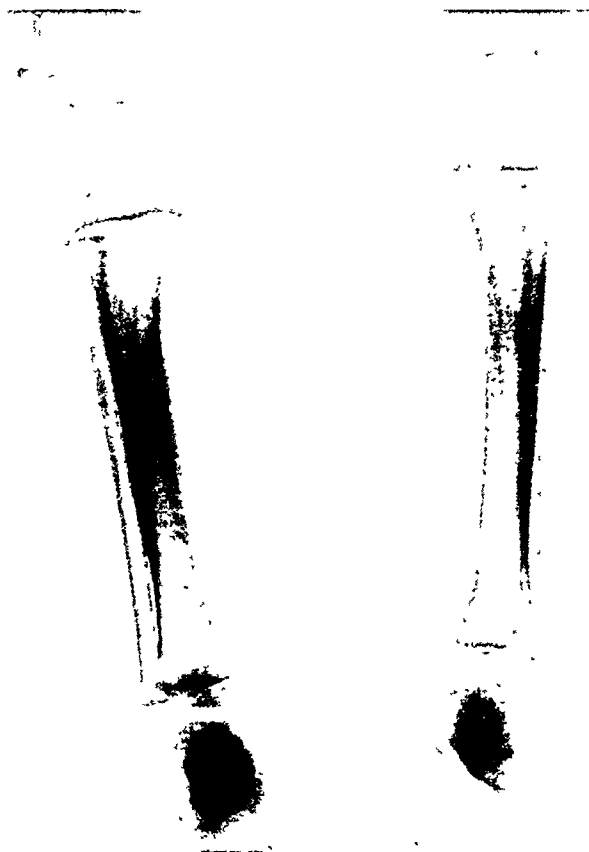


Fig. 3.—Roentgenogram of lower extremities taken July 3, 1946, shows considerable thickening of the periosteum along the shafts of the tibia and fibula, bilaterally.

On October 12, streptomycin therapy was begun, using 25 mg. per kilogram per day.

On October 19, the patient was transferred to Babies' Hospital for special thoracic surgery.

**Transfer Diagnosis.**—(1) chronic pyopneumothorax, right side, and (2) hypertrophic pulmonary osteoarthropathy was the diagnosis.

**Laboratory Data.**—Wassermann and Mazzini blood reactions were negative; urinalyses were repeatedly negative.

April 4, 1946, the red blood cells were 3,100,000; hemoglobin, 11.0 Gm.; white blood cells, 8,000; neutrophils, 40 per cent; lymphocytes, 40 per cent; monocytes, 12 per cent; and lymphoblasts, 8 per cent.

May 11, blood cholesterol was 106 mg. per cent; cholesterol ester, 66 mg. per cent; and albumin globulin ratio, 3.2/4.3.

May 24, the blood culture was negative. Repeated blood cultures on several later occasions were negative.

May 25, the Congo red test was 62 per cent present in serum after one hour.

July 30, red blood cells were 4,700,000; hemoglobin, 11.0 Gm.; white blood cells, 13,250; neutrophils, 20 per cent; lymphocytes, 76 per cent; eosinophiles, 2 per cent; monocytes, 2 per cent; numerous toxic granulocytes were noted.

September 18, red blood cells were 4,600,000; hemoglobin, 11.0 Gm.; white blood cells, 25,000; neutrophils, 11 per cent; lymphocytes, 81 per cent; monocytes, 7 per cent; basophiles, 1 per cent; numerous toxic granulocytes were noted.

### CONCLUSION

1. The rarity of hypertrophic pulmonary osteoarthropathy in children is noted, together with a brief review of the literature of the condition.

2. A case history is presented of a 2-year-old child having chronic pyopneumothorax, associated with hypertrophic pulmonary osteoarthropathy.

The authors wish to acknowledge their gratitude to the Pediatrics Department, City Hospital, New York, for their cooperation in the production of this paper.

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## FATAL SICKLE CELL ANEMIA IN A ONE-MONTH-OLD INFANT

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SINCE Herrick<sup>1</sup> first described the entity of sickle cell anemia in 1910, recurring reports have appeared in the American literature discussing the disease, its appearance, its manifestations, and the outcome. It is not the purpose of this paper to review the disease in its entirety, but rather to emphasize the occasional early onset and to re-emphasize the criteria for diagnosis.

A differentiation must be made between sickle cell anemia with crisis and "sicklemia," the sickling trait without anemia. Sicklemia is characterized only by the appearance of true sickle cells in sealed moist blood preparations without any hematologic evidence of anemia or any constitutional evidence of increased blood destruction. The incidence of sicklemia has been described as occurring in from 5 to 10 per cent of American Negroes.<sup>2</sup> Not more than 10 per cent of such individuals went on to develop the associated anemia. Sydenstricker<sup>3</sup> did not encounter an instance of sicklemia in a series of over 1,000 white individuals, and has reported an incidence of the sickling trait in 7 per cent of 1,000 negroes examined. In the outpatient department of Babies' Hospital<sup>4</sup> the blood of 150 Negro patients was examined, and thirteen or 8.6 per cent showed latent sickling, while the blood of white children did not show this phenomenon. Cooley<sup>5</sup> found 7.5 per cent incidence of sicklemia among Negroes in Detroit. Despite the failure to demonstrate the occurrence of the sickling trait in pure white persons when mass surveys were conducted, isolated cases of sickle cell anemia in patients of undoubted white heritage have been reported from time to time.<sup>6-8</sup> Elliptocytosis of the red blood cells, with and without an associated anemia, has been described as occurring with a familial incidence in white people. This must be differentiated from the true sicklemia and sickle cell anemia. The condition was originally described by Dresbach in 1904, and lately has been extensively reviewed by Lambrecht,<sup>9</sup> Wyandt and associates,<sup>10</sup> and by Huck.<sup>11</sup>

Sickling has been reported at all ages, and in the neonatal period.<sup>2</sup> Mulherin<sup>12</sup> examined the peripheral and cord blood of two infants whose mothers were suffering from sickle cell anemia, and found typical sickle cells. The peak incidence is during childhood, with a sharp decline following adolescence. There have been some cases reported during infancy, the youngest of which was reported by Wollstein and Kreidel<sup>4</sup> at 3 months of age. Branch<sup>13</sup> reported a case in a 6-month-old infant. Experience has shown that the earlier the onset occurs, the more severe is the disease and the poorer is the ultimate prognosis. While intercurrent infection is the most common cause of death in young children with the disease, Wollstein<sup>4</sup> feels that, in some fulminating cases, death may be caused by the anemia, *per se*.

The criteria for the diagnosis of sickle cell anemia are those for the diagnosis of any acute and chronic hemolytic anemia with the addition of demonstrable sickling of the erythrocytes, more commonly in incubated wet preparations and occasionally, where the disease is severe, in the stained blood film. Other causes for hemolysis should be excluded. It is a heredofamilial disease transmitted as a Mendelian dominant, subject to crisis and spontaneous remissions. The diagnosis of sicklemia may be established by demonstration of the

typically misshapen erythrocytes in wet blood preparations after twenty-four hours, and by the confirmatory differential sedimentation rates of oxygenated and carbon-dioxide saturated specimens of venous blood as described by Winsor and Burch.<sup>14</sup>

A case of sickle cell anemia in crisis with fatal termination in a one-month-old female Puerto Rican infant is presented.

J. C., a one-month-old Puerto Rican girl, was admitted to the Pediatric Service of Lincoln Hospital for fever and incessant crying of one day's duration. She had been a premature baby with a birth weight of 5 pounds and 2 ounces. Following an uneventful ten-day neonatal course in the premature nursery of this hospital, during which she had gained 8½ oz., she had been discharged home. On readmission her weight was 6 pounds and 12 ounces. On physical examination a red and moderately bulging left eardrum was seen. Temperature was 102.4° F. The leucocytes numbered 13,200 per mm.<sup>3</sup> with 66 per cent polymorphonuclears and 34 per cent lymphocytes. Hemoglobin was 11.5 Gm. per 100 c.c. by the Sahli method. Urinalysis showed two to three erythrocytes and one to two leucocytes per high power field of a voided specimen. The urine was negative for albumin, glucose, and acetone. The day after admission, the left ear began to show a watery, white, purulent discharge. The temperature rose to 104.4° F. She was started on intramuscular penicillin, 10,000 units immediately followed by 5,000 units every three hours. The following day the temperature was 103.0° F. and the discharge from the ear continued. Sulfadiazine, 0.1 Gm. every four hours, was begun. Because of questionable nuchal rigidity, a lumbar puncture was done and completely normal spinal fluid was recovered. On the following day, the fourth day of hospitalization, the patient was observed to be jaundiced. Examination of the blood at that time showed the following: red blood cells, 2.24 million per millimeter;<sup>3</sup> hemoglobin, 5.5 Gm. per 100 c.c.; hematocrit, 23 per cent; white blood cells, 26,200 per millimeter<sup>3</sup>; polymorphonuclears, 26 per cent, lymphocytes, 68 per cent; monocytes, 6 per cent; and nucleated red blood cells, 2 per 100 leucocytes. The red cells were normochromic with mild anisocytosis and poikilocytosis. No spherocytes were seen, but there were occasional target cells. Urinalysis showed urobilinogen to be present in 1:5 dilution but bile could not be detected. The benzidine test for blood was 4 plus, and 15 to 20 red blood cells per high power field were observed on microscopic examination. Bleeding time was 4 minutes, 20 seconds, and the clotting time was 1 minute, 10 seconds. The blood Van den Bergh reaction was immediate direct and the icterus index was 130 units. The cephalin-cholesterol flocculation test was plus-minus. The patient was given a transfusion of 50 c.c. of typed and cross-matched Rh-positive, type O, citrated whole blood. The sulfadiazine was discontinued. On the fifth hospital day, the stained blood film showed many typical sickle cells. A moist preparation then showed marked initial sickling and 80 per cent sickling after incubation for twenty-four hours. No cold hemagglutinins could be demonstrated. The parents were blood-typed with the following results: mother was type A, Rh-positive, and father was type B, Rh-positive. The fever persisted at about 102.4° F. and the left ear continued to drain. On this day the hemoglobin was 7.0 Gm. per 100 c.c. and there were 2.08 million red blood cells per millimeter.<sup>3</sup> Examination of the stained tibial marrow performed on the seventh day revealed marked sickling of the erythrocytes. At this point all available members of the patient's family were called in and moist blood preparations were done on each. There were both parents, the sole sibling, and a maternal uncle, none of whom showed sickling after twenty-four hours, nor could any familial history of anemia be obtained. On the eighth day, the hemoglobin was 6.5 Gm. per 100



c.c. and there were 2.45 million red blood cells per millimeter.<sup>3</sup> The ear had returned to normal by the ninth day, and, as the baby had been afebrile for the previous two days, penicillin was discontinued. The hemoglobin was 5.5 Gm. and there were 1.24 million red blood cells. Transfusion of 90 c.c. of citrated whole blood was done. The temperature remained normal and the child ate well until the twelfth hospital day, when the temperature again rose to 103.8° F. Physical examination at this time was negative except for the persistence of the icterus. The temperature returned to normal in two days without treatment. On the fifteenth day the child began to have diarrhea and to refuse feedings. A moist preparation of the peripheral blood made at this time showed marked sickling. The next day she was observed to moan constantly and seemed to have an expression of anxiety and pain. There was a gross increase in the degree of jaundice. A tubular mass could be palpated emerging from under the inferior edge of the liver in the right upper quadrant and descending to within 2.5 cm. of the level of the umbilicus. Hemoglobin was 9.5 Gm. and there were 3.05 million erythrocytes. Leucocytes numbered 19,900, of which 78 per cent were neutrophiles. Fully realizing that this development might be a manifestation of the sickle cell crisis, still the possibility of a surgical abdomen could not be ruled out. Later the same day, the skin overlying the mass became reddish-blue and the child began to exhibit symptoms of respiratory distress. Surgical consultation was obtained and a laparotomy was decided upon. After supportive therapy by whole blood transfusion and intravenous electrolytes, the abdomen was explored. Large mesenteric lymph nodes were the only abnormalities found. The downhill course continued postoperatively and exitus occurred after six hours.

On autopsy, it was seen that the child was markedly icteric. There were numerous ecchymotic areas over venipuncture sites.

The trachea showed an edematous and congested mucosa. The lungs were pinkish-grey in color with many whitish areas over all surfaces. These areas were from one to 10 mm. in diameter and slightly raised above the surrounding surface. On section, the whitish plaques were seen and the alveoli and smaller bronchi exuded a whitish—reddish—yellow thin fluid. The esophagus had a yellowish-gray mucosa, and, in its lower third, there were numerous areas of punctate hemorrhage. The pericardial sac contained some bile-stained fluid. The heart was of normal size, but very pale pink in color. The myocardium, on section, was pale.

On opening the abdominal cavity, the intestines were seen to be distended. Numerous areas of hemorrhage were seen throughout the serosa. The liver was slightly enlarged, and, on section, exhibited a pale brown parenchyma with bile-stained canaliculi. The spleen was slightly enlarged, had a thin, smooth capsule, was reddish purple in color, and had a firm consistency. On section of the spleen, a mottling was observed with areas of brown and deep red coloration. The stomach contained about 50 c.c. of chocolate-colored viscid fluid when opened. The mucosa was grayish, had engorged vessels, and showed numerous punctate hemorrhages. The small bowel showed moderate injection of the mucosal vessels. At the terminal end of the ileum were noted small grayish discrete areas disseminated over the mucosa and continuing into the large bowel as far as the distal portion of the descending colon. The kidneys were enlarged, grayish-yellow in color, with many wedge-shaped dark purple areas. Punctate hemorrhages were found all over the cortical surfaces. When sectioned, the pyramids and papillae were found to be bile stained. There were thromboses of the interlobar arteries. Areas of bipolar infarction were seen in both kidneys. The adrenals showed hyperemic medullae. The mesentery was greatly injected.

The lymph nodes were enlarged, but showed no gross invasive tendencies. There was a marked hemorrhagic cystitis of the bladder trigone, and spotty small hemorrhages of the rest of the bladder mucosa. The ureters were greatly dilated and hypertrophied, with a swollen ostia and diffusely thickened purplish-red hemorrhagic mucosa. There was a stenosis of the ureteropelvic junction on the left side.

Microscopic examination of sections of the spleen and kidney showed occasional typical sickle cells. Dr. Peter Vogel, the consulting hematologist to this service, who examined the tissue sections and the films of the peripheral blood and tibial marrow taken during life, confirmed the presence of typical sickle cells.

#### COMMENT

We have presented a case of sickle cell anemia. Two unusual features combine to make this case worth reporting. The first feature, the early onset at one month of age of sickle cell anemia in crisis, has not been previously described. It is likely that the hemolytic crisis in this case was precipitated by an infectious process, acute purulent otitis media. While chemotherapy and penicillin controlled the infection in a reasonable period of time, yet once the hemolytic process had been established, its course became rapidly progressive despite supportive therapy. The second noteworthy feature was the disparity between the amount of sickling observed in the early wet preparations during life, when 80 per cent of the red blood cells sickled in twenty-four hours, and the later wet preparations and the tissue sections obtained post mortem. In the latter, while some sickling was obvious, it was much less in degree than previously. It may be that the transfusion of normal erythrocytes plus the hemolysis of the patient's cells so diluted the abnormal forms as to account for this apparent decrease in the percentage of cells showing sickling. On a quantitative basis, the child's blood volume has been calculated as about 400 c.c. and the amount of whole blood transfused into the patient was measured at 315 c.c. Thus it may be seen that better than 75 per cent of the patient's blood volume at the time of death consisted of normal cells. All the transfused blood was freshly drawn and may be considered to have an expected viability of at least thirty days, about twice the period over which the transfusions were given.

The accessory evidence of a hemolytic process, essential for the diagnosis of sickle cell anemia in crisis, was present in our patient. The rapid reduction of hemoglobin content of the blood from 11.5 Gm. on admission to 5.5 Gm. on the fifth hospital day; the development of concurrent clinical and laboratory evidence of marked icterus; and the plus-minus cephalin-cholesterol flocculation test are indicative of rapid hemolysis and jaundice of extrahepatic origin. In passing, it should be remarked that sickle cell anemia in crisis is not infrequently accompanied by symptoms and signs referable to the abdomen and simulating an acute surgical emergency. In our case the masquerade was so effective that laparotomy was done. We have purposely refrained from commenting upon or stressing the patient's race because of the impossibility of accurately evaluating its true status.

#### SUMMARY

A case of fatal sickle cell anemia in crisis in a one-month-old Puerto Rican female infant has been presented. The development of the hemolytic crisis followed the occurrence of an acute purulent otitis media. Clinical and laboratory evidence confirmed the diagnosis.

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## ENCEPHALITIS ASSOCIATED WITH HERPES ZOSTER

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POSTINFECTIOUS encephalitis complicating the acute exanthematous diseases is a relatively common occurrence, but encephalitis associated with herpes zoster is a rare event, even though the close relationship between the virus of chicken pox and that of herpes zoster has been recognized for some time. The following case is, therefore, of interest.

T. S., a white male child, aged 6 years, was admitted to St. Vincent's Hospital, Staten Island, on Aug. 7, 1946, with complaint of drowsiness, paralysis of the right side of the face, and weakness of the right leg. He had been well until four days prior to admission, when he began to run a low-grade fever and to complain of frontal headaches. On the day before admission, the mother had noticed a "rash" on both buttocks. These symptoms continued until the day of admission, when the right facial paralysis and weakness of the right leg was noticed and the family physician recommended hospitalization.

On examination, a fairly well-nourished and well-developed boy was noted, who appeared to be only moderately ill. The temperature was 101.6° F., respirations were 30 per minute and pulse was 120 per minute. The patient appeared to be quite restless, but was yawning constantly. Although he seemed quite alert, he was able to answer only yes or no to questions. There was right facial palsy and a positive Babinski reflex on the right side. The fundi were hyperemic, but otherwise normal. Herpetic lesions were present on both buttocks in areas corresponding to the cutaneous distribution of the second and third sacral segments. The spinal fluid was clear and showed no increased pressure. The cell count was 0, Pandy test was negative. The sugar was 50 mg. and the chlorides 660 mg. The red blood count and hemoglobin were normal, but the leucocyte count was 3,700 per c.mm. with the following distribution: small lymphocytes 14 per cent, mononuclears 6 per cent, polymorphonuclear neutrophils 79 per cent, and plasma cells 1 per cent. The spinal fluid Wasserman and colloidal gold tests were negative. The urinalysis was also negative.

On the following day, in addition to the above findings, the patient exhibited a complete right hemiparesis, as well as incontinence of urine and feces. Another spinal fluid examination showed no abnormal findings. A diagnosis of a Strumpel-Lichtenstern encephalitis associated with herpes zoster was made. Treatment consisted of intravenous hypertonic glucose, as well as intensive vitamin B complex and vitamin C therapy.

The patient continued to run a low-grade temperature for a week. A Voller patch test was negative. Three days after admission, the superficial and deep reflexes returned on the right side, and on the next day he began to move his right arm and leg, although the right Babinski reflex was still present. The right facial paralysis was less pronounced and the incontinence was no longer absolute.

The patient was discharged to his home for further convalescence eighteen days after admission. A physiotherapeutic regime of massage, galvanism, and active and passive exercise of his right arm and leg was instituted. He was seen one month after discharge. It was noted that he was walking, but did not have complete range of motion of his right foot. The right fingers were flexed and spastic and he had difficulty in moving them and in grasping. The right facial palsy had nearly cleared. He still showed a moderate motor aphasia, but no

sensory aphasia. It is felt that it is too soon to evaluate this case as to the degree of permanent paralysis, Parkinsonism, behavior problems.

Of interest in the case is an apparent familial susceptibility to a neurotropic virus. Two days after this patient was admitted to the hospital, the family physician reported that another sibling, aged 2 years, had developed bilateral herpes zoster over the same areas as her brother. This did not progress to a clinical encephalitis. In May, 1946, a first cousin of the patient, a white male child aged 11 months, died of a measles encephalitis after an illness of about a week.

A cursory review of the literature does not reveal any case reports of this syndrome occurring during childhood. The case reported by Krumholz and Luhan<sup>1</sup> was that of a 58-year-old woman. Thalhimer's<sup>2</sup> patient was 72 years old and Biggart's and Fisher's<sup>3</sup> was 63 years old. The only case with comparable sequelae was the one reported by Bellavitis<sup>4</sup> in a psychotic patient age 53 years, who had suddenly developed herpes zoster in the distribution of the second to the fourth cervical segments on the left side. Eight days later, palsy of the peripheral type developed on the same side of the face and a few days later hemiparesis developed on the left side. In all of these cases, cerebral symptoms developed more than a month after the onset of the herpes, in contradistinction to our patient, whose cerebral symptoms coincided with the onset of the eruption.

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# The Academy Study of Child Health Services

## A REVIEW OF PROGRESS AND A PREVIEW OF PLANNING

Having been present when the Academy's Study of Child Health Services was first placed upon the planning boards, having attended its launching upon rather uncertain seas at the annual meeting in Detroit early in 1946, and having watched its development from the position of sponsor and adviser, it seems appropriate and timely to review its progress and also to gaze into the crystal in an attempt to see where we may be at the end of another year.

Annual meetings of the Academy present an excellent opportunity to take stock of the progress which has been made and to build upon the steps already surmounted, others leading toward further endeavors. The meeting held recently at Pittsburgh emphasized two significant facts. First, the Academy's Study had grown far beyond the anticipations which even its most enthusiastic proponents originally expressed. Second, the efforts of its members, both singly and collectively, during the preceding year had brought the Academy into a position of prominence and responsibility which demanded energetic planning if it is to make full use of the wealth of factual data now becoming available.

A little over one year ago, at our meeting in Detroit, Dr. John Hubbard, who had only a short time before been appointed director of the Academy's Study, brought before the meeting the plans which had been evolved to launch this project upon a nation-wide scale. The responsibility of obtaining the desired information was placed in the hands of State Chairmen. This responsibility was accepted with considerable misgiving. Indeed, there were those who questioned if the job could be done at all. Now, however, although the Study is not completed, it has gathered such momentum that it would be impossible to stop it. It was reported at Pittsburgh that the Study had been organized and was being successfully pursued in all States, including the District of Columbia and the Territory of Hawaii, with the single exception of one State, which it is hoped will follow soon. About a dozen States have completed the collection of information and have sent their questionnaires to the Central Office for statistical analysis. It is expected that all States will complete the collection of information by July of this year.

The first tangible results of the Study came to light at Pittsburgh in the form of a weighty volume which was distributed as a preliminary draft of the Study of Child Health Services in North Carolina, our "pilot" State. This was put into the hands of the Executive Board, the Academy Committee, and all State Chairmen who attended the meeting. It has since been distributed to all members of the North Carolina Pediatric Society. On March 12, 1947, it was the subject of a lengthy conference at a meeting of the Advisory Committee. It now becomes the responsibility of the pediatricians of North Carolina and a committee which they have appointed to reduce the overwhelming mass of factual data to more appropriate dimensions and to prepare the recommendations intended to serve as a basis for a continuing program.

While the State Studies have been reaching successful completion, the second main division of the Academy Study, the Study of Pediatric Education, has been developed under the able direction of Dr. John Mitchell. Regional meetings, which have been held throughout the country by Dr. Hubbard and Dr. Mitchell, have been attended by the chiefs of pediatric departments in their respective areas in order to introduce to them the plans and purposes of this phase of our work. Personal visits have now been made to about half of the medical schools and the major teaching hospitals of the country. From these visits a wealth of information is pouring in to the central office of the Study. When this material is analyzed and summarized, it should afford a composite and yet detailed picture of pediatric education never before available.

At this point, with the success of the Study assured and with the data on all phases of child health services well along the way toward analysis, the most important question of all demands an answer. What is to be done with all this information when it has been summarized in a final report? It is no mere coincidence that a new committee of the Academy has already been formed and charged with the responsibility of writing an answer to this question. As long ago as last fall, Dr. Lee Forrest Hill, then President-elect, recommended, first in a meeting of the Committee for the Study of Child Health Services, and shortly thereafter in a meeting of the Executive Board, that this new committee should be appointed without delay, in order that it might overlap with the Study committee and serve as a continuing committee for the implementation of the Study. This new committee, which is to be designated as the Committee for the Improvement of Child Health, met in joint session with the old committee at Pittsburgh. At this meeting, the Academy projected its planning to the point when an action program may be developed upon the basis of the survey material. Thus the Academy has demonstrated that it has recognized its increased responsibility and has given assurance that it has every intention of making proper use of the available information at both State and National levels. The policies and procedures which have been established to govern the reporting and implementing of the Study have been expressed in the following series of recommendations which were drawn up by the Committee for the Study of Child Health Services, submitted to and approved by the Executive Board in November, 1946:

1. That all factual material arising from the Study of Child Health Services should be released by the American Academy of Pediatrics at both National and State levels.
2. That the Committee for the Study of Child Health Services is responsible not only for preparing a National Report of the factual material but also for submitting to State Chairmen tabulated factual data suitable for the preparation of State Reports.
3. That State Chairmen, together with their Advisory Committees, are responsible for seeing that State Reports based upon the tabulated material are written and published as soon as possible. Whereas the National Report prepared by the Committee for the Study of Child Health Services will include no recommendations arising from the data, the State Reports may and should include recommendations based upon local situations.
4. That when the tabulated material is received by the State Chairman he will confer with the State Medical Society, the State Dental Society, and the State Health Department regarding the interpretation and use of the material, in those States where these agencies have cooperated in the conduct of the Study.
5. That within a period of two months after receipt of the tabulated material, State Chairmen should be required to submit to the Committee for the Study of Child Health Services a statement indicating that definite plans have been made to write a State Report and a brief description of such plans. If, at the end of this two-month period, the State Chairman has not made satisfactory plans to report the material arising from the Study in his State, the Committee for the Study of Child Health Services is free to release the factual data to any person or group qualified to use it within the State. If the plans for the preparation of the State Report are considered by the Committee to be satisfactory, then the State Chairman should be allowed an additional period not to exceed four months to complete the State Report, during which time none of the factual data pertaining to his State should be released to others by the Committee for the Study of Child Health Services except after obtaining approval from the State Chairman concerned.
6. That after a period of six months following the receipt by the State Chairmen of the tabulated material, the Committee for the Study of Child Health Services is free to release the tabulated material or punch cards to any person or group qualified to use it.
7. That a further Committee of the Academy should be created which would be responsible for the recommendations arising out of the Study at the National Level and for developing from the Study a suitable action program. This committee would

- also be responsible for reviewing the recommendations contained in State Reports, advising in the use of the material in the respective States, but would have no veto power over any recommendations in State Reports.
8. That in the case of North Carolina, the pilot State, the Committee for the Study of Child Health Services should be responsible not only for the factual report but also for reviewing the recommendations contained therein.
  9. That in publication of State as well as National Reports, credit should be given to the United States Public Health Service and the Children's Bureau for the co-operation they have given to the Academy in the Study. Acknowledgment should also be made of contributions or cooperation in the form of services and financial support from other sources.
  10. That after publication of National or State Reports the factual material should be available to anyone desiring to use it.

As a member of the Committee on Child Health Services and as a resident of Washington, it has been my privilege to know rather intimately of the work of the Study from its early inception up to the time of this report. As an observer in this strategic position, it is gratifying to record and emphasize the remarkable spirit of cooperation and accord which permeates the whole Study group, now numbering several score.

Furthermore, the Study represents a rather unique and original experiment in the active cooperation of governmental agencies with a purely voluntary organization, not for the individual aggrandizement of any component, but toward the attainment of a common goal "for the improvement of child health," a purpose made dynamic by the very phraseology of the term, which has wisely been chosen as the caption for the newly appointed continuation and action committee of the Academy.

At its St. Louis meeting, the Academy unanimously decided to embark upon this nationwide investigation of the needs of children and to develop the ways and means of meeting them.

With the realization that the Study was to be conducted by pediatricians in the interest of children and pediatrics, it became apparent from the onset that aid would be imperative from professional members of governmental agencies who were skilled in the techniques of exploration in the field of child health.

By direction of the original resolution adopted by the Academy, the Children's Bureau and the U. S. Public Health Service were asked to lend assistance, which was instantly and generously granted on the part of both agencies. Any misgivings on the part of pediatricians or other physicians (and there have been some) that the participation of governmental agencies in the undertaking at hand inferred ulterior motives of dominance in the field of health services to children would be set at rest were such questioners familiar with the facts. The outstanding fact apparent to the Academy's committee is that the successful completion of the Study would have been utterly impossible had it not been for the contribution of that endowment of expert knowledge, that "know-how" of trained investigators and statisticians (which not even the most robust academician could justly claim to possess) generously given us by the assisting agencies.

In monetary value of services rendered alone, this represented thousands of dollars aside from the substantial financial aid of the grants which have been received.

One outcome of the Study stands forth as a prophetic omen for the future, namely, the accord and harmony which may and should be the bond of cooperation among all who labor for the improvement of the health of children and for the progress of pediatrics which is their servant.

The Study of Child Health Services started as our responsibility; it continues as our opportunity.

JOSEPH S. WALL, M.D.



# The Social Aspects of Medicine

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Dr. Ernst P. Boas of New York, N. Y., chairman of the Physician's Forum, has been kind enough to reply to Mr. W. A. Milliman's "Compulsory Prepaid Medical Care" (J. Pediat. 29: 527, 1946). Mr. Milliman's article should be reviewed in order to understand fully Dr. Boas' answer.

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E. A. P.

## COMPULSORY PREPAID MEDICAL CARE

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*Compulsory prepaid medical care under governmental auspices is a technique of providing medical care to all the people. Intelligent discussion of this controversial subject involves a consideration of the basic social philosophy that has persuaded many persons that good medical care should be universally available, as well as an evaluation of the feasibility of assuring good medical care to all by means of this method.*

During the past decades, the public, the recipient and purchaser of medical care, has become ever more aware of the potentialities of modern medicine in the prevention and treatment of disease, and has become ever more articulate in demanding that this great social service be made available to all, irrespective of income or buying power. This view has been given forceful expression in Franklin D. Roosevelt's new Bill of Rights in which "The right to adequate medical care and the opportunity to achieve and enjoy good health" are laid down as basic human rights. This paper is based on an acceptance of the tenet that availability of medical care is a fundamental human right.

It has been well established that good medical care is out of reach of large numbers of our citizens because it is beyond their financial capacity. This is not the place to present the voluminous factual data to support this statement, they are readily available to all who wish to seek them out. Mr. Milliman, in his recent article, "Compulsory Prepaid Medical Care" concedes that much of this is true. Unless we regard medical care as a luxury, which people may or may not obtain, depending on their ability to pay for it, we are faced with the compelling problem of how to make it available to all, irrespective of income. It is at this point that many persons leave the cold path of logic, and, rationalizing their fear or dislike for an extension of governmental responsibility, seek to find a solution in halfway measures, such as the establishment of voluntary health insurance schemes, and the construction by government of hospitals and diagnostic centers.

Yet, the role of government in preventing disease and treating the sick is an ancient one. No one today challenges the duty of government, through its public health agency, to continue to marshal every resource to prevent epidemics and control infectious diseases. No one would wish government to cease providing medical care for the indigent, and for patients with certain chronic diseases, whose course is so long drawn out that the patients and their families cannot afford to pay for this care. I refer to mental illness and tuberculosis.

The diseases responsible for most sickness and deaths today are no longer the infectious diseases such as typhoid fever, tuberculosis, and the acute exanthemas. They are diseases obscure in origin and chronic in their course, such as the several forms of heart and arterial diseases, diabetes, cancer, rheumatoid and other forms of arthritis. None of the conventional methods of preventive medicine will ward off any of these disorders. The public health officer is learning that in order to control their ravages—for in the present state of medical

knowledge their prevention is still beyond the range of medical science—the most potent weapon is immediate and ready accessibility to medical care, both for diagnosis and treatment. This is why thinking health officers have become deeply concerned with the quality and availability of medical care, and why many of them do not hesitate to advocate radical changes in the economic pattern of medical practice. Fundamentally, this, too, is not a new concept. In his attempts to prevent tuberculosis and venereal diseases, the health officer has been compelled to undertake the treatment of sufferers from these diseases. Indeed, he has gone further, and, by examining the families and others who have had contact with victims of these diseases, has offered diagnostic and therapeutic services to persons who were presumably well, all in the effort to prevent disease.

The changing face of disease, brought about by the rapid and efficient control of the infectious diseases, has brought about a new and necessary reorientation of public health activities. If making medical care readily available to all will help to control the rapid evolution of some of the chronic diseases and maintain many persons as useful economic units of society, there is every reason for government to concern itself with the problem through the agency of its public health services.

This need not involve total regimentation of medical services in the nation, or complete shedding of personal responsibility for the maintenance of individual health. But government must assume leadership, provide facilities of public education in disease control and the utilization of medical facilities, and collect and administer the funds that are needed to provide adequate medical care for all.

If we face the changing order in medicine and in society with realism and honesty, we must seek to discover by what methods good medical care can be made available to all inhabitants of this country. Mr. Milliman suggests that the best progress in improving preventive medical care would be achieved by further emphasizing medical research, by improving facilities for medical education, and by expanding and improving existing public health services. He does not indicate from where funds for these purposes will be obtained. He also advocates the development of diagnostic centers financed in part by public funds, in part by charity, in part by charges for services. He suggests further experimentation with voluntary plans for prepayment of medical costs, the development of a more constructive attitude by the medical profession, and experimentation with group practice. These all are excellent suggestions as far as they go.

Funds for research for medical education have been derived largely from philanthropic foundations and from wealthy donors in the past generation. It is apparent that this source is rapidly becoming inadequate to meet the growing needs. Lower interest rates on capital funds, and greater taxation have greatly decelerated the growth of fortunes. Ever greater dependence must be placed on tax funds.

Voluntary prepayment insurance for medical care can never meet the needs of the bulk of the population. This has recently been forcefully demonstrated by Goldman.<sup>2</sup> He shows that, judged by the criteria of the provision of early diagnosis and treatment, completeness of medical care, quality of service, and cost to the patient, only the few voluntary prepayment plans organized on the basis of group practice are making real progress or rendering good service. The large majority of prepayment plans, in which the individual doctor is compensated for certain individual services that he renders, are nothing but financial arrangements for payment of bills, and do not improve the quality of medical care. A good prepayment plan for complete medical services given through group practice units costs from \$25 to \$30 a year per person—a price beyond the reach of many heads of families. It is interesting to recall that the minority report of the report of the Committee on the Costs of Medical Care, signed by representatives of the American Medical Association stated: "Nothing has been made clearer than the fact that voluntary insurance schemes have everywhere failed. It seems clear, then, that if we must adopt in this country either of the methods tried out in Europe, the sensible and logical plan would be to adopt the method to which European countries have come through experience, that is, a compulsory plan under government control."<sup>2</sup>

# Academy News and Notes

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## THE FORMATION OF THE BRAZILIAN BRANCH OF THE AMERICAN ACADEMY OF PEDIATRICS

In May of 1942, Dr. Adamastor Barboza, at that time in Washington, D. C., as delegate of Brazil at the Eighth Pan-American Child Congress, arranged with the secretary of the Academy to extend activities of the Academy to all South American countries and ask for the concerted help of Brazilian pediatricians toward this end. It was agreed that at a suitable time in the immediate future, the plan then being elaborated by the Academy should be reconsidered.

The names of a few Brazilian pediatricians were submitted for acceptance as active members in the Academy with exactly the same privileges and duties as the North American members. The qualifications for eligibility to fellowship were the same as those observed for all regions of the Academy: (a) professional integrity; (b) activity exclusively in pediatrics, in practice, teaching, or public health work, or combinations of these; and (c) at least five years of practice in pediatrics.

Two types of annual dues were set up provisionally. One of these is \$5.00, including the member's privilege to receive in Spanish abstracts from two main American reviews on pediatrics—"The Journal of Pediatrics" and "The American Journal of Diseases of Children." A second is \$10.00 with a full subscription to "The Journal of Pediatrics" and abstracts in English of the original articles published in "The American Journal of Diseases of Children." It was suggested that the second type already adopted by the pediatricians of Mexico would possibly be the more interesting.

The following list of pediatricians was submitted:

Dr. José Martinho da Rocha	Dr. Lages Netto
Dr. Leonel Gonzaga	Dr. Alvaro Aguiar
Dr. Mario Olinto	Dr. Carlos Florencio de Abreu
Dr. Cesar Pernetta	Dr. Adamastor Barboza

In November, 1942, a committee of five was formed whose function would be to pass upon the qualifications of any wishing to apply for membership in the Academy. In order to link the activities of the Brazilian Committee of the Academy with the Sociedade Brasileira de Pediatria, a conference was held with Dr. Vicente Lara, President of the Pediatrics Division of the Medical Association of São Paulo, suggesting the possibility of the formation of a mixed committee with representatives from both the Sociedade Brasileira de Pediatria and its sister Society in São Paulo.

A subcommittee consisting of Dr. Adamastor Barboza, Dr. Eduardo Imbassahy, and Dr. Alvaro Aguiar was formed. This committee decided unanimously to form a Brazilian Committee of the American Academy of Pediatrics, whose membership should be chosen from the eight pediatricians recently suggested to the Academy. To avoid any partisanship, it was decided to limit the choice to those who had already filled the post of president of the Sociedade Brasileira de Pediatria.

As a result, the first Brazilian Committee of the Academy consists of the following members:

Dr. José Martinho da Rocha  
Dr. Mario Olinto  
Dr. Cesar Pernetta  
Dr. Leonel Gonzaga  
Dr. Adamastor Barboza

One of our members, Dr. José Robalinho de Oliveira of Pernambuco, Brazil, died recently.

## News and Notes

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### MEMORIAL HOSPITAL FOR CANCER AND ALLIED DISEASES ANNOUNCES AN EXTENSION OF ITS CHILDREN'S DIAGNOSTIC SERVICES

An extension of the diagnostic service of the Children's Tumor Registry of Memorial Hospital was made on Jan. 1, 1947, with the establishment of the Children's Diagnostic Clinic. This service is offered to the pediatric patients of hospitals and private physicians for the diagnosis of neoplastic diseases, and is available for ambulant or bed cases. The investigations will be performed at cost or without charge if the patient is unable to afford this. Upon completion of the study the patient will be referred back to the physician or institution interested, with a report of the findings. If therapeutic recommendations are indicated and requested they will also be made.

Appointments for such examinations may be made by mail or telephone with: The Secretary, Pediatric Service, Memorial Hospital, 444 East 68th St., New York 21, N. Y.

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### NOTICE

Due to the increased cost of running the *American Board of Pediatrics*, the board has found it necessary to raise the application fee to \$125.00, effective May 1, 1947.

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## Book Review

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**The Challenge of Polio.** R. H. Berg, New York. 1946. The Dial Press.

This little volume, written under the auspices of the National Foundation for Infantile Paralysis by a nonmedical, professional science-writer, serves its primary purpose fairly satisfactorily, which is to acquaint the public with the problem of poliomyelitis in a readable style. While, like most other attempts to present scientific or medical subjects for lay readers, the book leaves one with a feeling of dubiousness regarding some of the contributions singled out for special emphasis, it impresses the reviewer as being fair and authentic on the whole.

The historic development of our knowledge of the disease, the discovery of its cause, studies on its epidemiology or mode of spread, and the attempts to find effective means for its prevention and treatment are interestingly reviewed. One fact brought out which should arrest the attention of the professional as well as the lay reader is that severe epidemics of poliomyelitis were not known before the latter part of the nineteenth century. The author makes it clear that the increasing frequency of severe epidemics during the past thirty years presents a grim challenge to medical scientists. While the conspicuous gaps in our knowledge are clearly pointed out, recent advances are presented in a hopeful light. The appraisals of such controversial topics as the Kenny concept and treatment of poliomyelitis and neurotripty are rational and without emotional prejudice.

From the pediatricians's viewpoint, the most glaring deficiency of the book, which is forsooth a reflection on current literature on the subject, is the almost total lack of reference to the 6 to 15 per cent mortality resulting from the acute disease. While space is freely devoted to consideration of the spinal paralytic type of case, no attention is given to the forms of the disease which result in respiratory and circulatory insufficiency or death and which terrify the physician as well as the patient and his family. The book's index does not include such terms as bulbar, cranial nerves, polioencephalitis, respiratory failure, respiratory muscles, diaphragm, intercostals, respirator, artificial respiration, pulmonary, atelectasis, edema, pneumonia, oxygen, anoxia, complications, or others that would indicate any insight into or interest in these more serious aspects of the disease.

I. McQ.

# Comment

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## THE FIFTEENTH ANNUAL MEETING

Despite the postponement of the Fifteenth Annual Meeting from last November to February 24-27 of this year, the Pittsburgh meeting was the largest, and in many ways the most successful, ever held by the Academy. The total registration was 1,363 with 589 Fellows in attendance.

Round Tables, which had to be discontinued in large part during the war, were again included in the program. There were four half-day sessions of ten round tables each. The panel discussions, which were held at the same time, were of unusual interest and well attended. In fact, there were so many things of interest going on at the same time it was difficult to make a choice of what session to attend.

At the annual business meeting, the Borden Award was given to Dr. James Gamble of Boston in recognition of his years of fundamental research in infant metabolism. The 1945 Mead-Johnson Award, which was not presented last year, was awarded to Dr. Paul Harper of New Haven in recognition of his work in malaria control in the Pacific Area during the war. The 1946 Award went to Dr. Horace Hodes, of Baltimore for his work on virus encephalitis during the war.

By a rather close vote, the plan presented last year was adopted for redistricting the Academy membership into nine districts of comparable membership size to replace the past division into four regions. Each district will have one member on the Executive Board. In place of the regional meetings, sectional meetings arranged by the central office will be held in different parts of the country. The next annual meeting will be held in Dallas, Texas, in December of this year, and the first of the sectional meetings in Salt Lake City, Utah, in September.

With Dr. Durand's retirement at the end of the meeting, Dr. Lee Forrest Hill assumed the presidency. Dr. John A. Toomey of Cleveland was elected President-elect.

Considerable time was given, in committee meetings and by the State Chairmen, to the Academy Study which is making rapid progress. A most important step was the announcement of a new committee headed by Dr. James Wilson to implement the results of the study. This committee of nine will have three-year terms with three new members annually. On its shoulders and those of the state chairmen will fall in large part the use that is to be made of the study.

With the Pepper Bill in the discard, there was nothing to upset the dispositions of the Fellowship, and, despite storms and late trains, many remarked that it was as good and successful a pediatric meeting as they had ever attended.

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## Original Communications

### PRESIDENTIAL ADDRESS

JAY I. DURAND, M.D.

SEATTLE, WASH.

A YEAR ago, Dr. Sisson and Dr. Hubbard presented the Academy with plans for the Study of Child Health Services. This survey was to extend into every county of our forty-eight states. It called for investigation and a report on the work of every hospital, institution, and health agency, and the practice of every doctor and dentist caring for children. They presented a budget calling for a million dollar expenditure. Most of us were staggered and rather terrified at the magnitude of the undertaking. Our state chairmen and members accepted the challenge. They have worked conscientiously and with increasing enthusiasm.

Today the greater part of the work has been done, and its successful conclusion is in sight. In taking just pride in this achievement, we must acknowledge our debt to the United States Public Health Service, the Children's Bureau, The National Foundation for Infantile Paralysis, the evaporated milk and drug companies, and other agencies, whose generous aid with funds and personnel have made it possible.

The Academy must now assume the responsibility imposed by the survey. We must study its findings and assume leadership in utilizing them for the improvement of the health of America's children. To this end the Executive Board has created a new committee, the "Committee for the Improvement of Child Health," which will direct the work. Nine members have been appointed, three for a term of one year, and three for two and three years respectively. New members will be named for three years of service as the terms of the present appointees expire. This will provide continuity, with frequent infusion of new blood. Every member chosen for this service accepted promptly, a fine expression of our organization's unselfish desire to undertake welfare work. In addition to this national direction, state or local committees will no doubt carry on in many districts.

The threat of extremely socialistic legislation which sought to make us subservient to Federal bureaus and take the direction of work for the "Health

Presented before the Fifteenth Annual Meeting of the American Academy of Pediatrics, Pittsburgh, Pa., Feb. 24-27, 1947.

and Welfare of Children" out of our hands seems measurably eased. We are grateful to our legislative committee and its able chairman, Dr. Wall, for valuable work toward this end.

The improvement in the health and nutrition of children since I began the practice of pediatrics thirty-five years ago, is not appreciated by younger graduates, and perhaps has been forgotten by some of the older men. In the early days of my practice half of the patients were so badly fed that at 3 and 6 months of age they were not much above birth weight. Rickets, with its resulting deformities, was universal. Summer diarrhea doubled infant mortality. Acute infections were not well diagnosed or treated.

The very rapid improvement in health conditions and reduction of mortality has been due to the education of pediatricians and their subsequent work. These specially trained physicians worked for the welfare of children: they crusaded for clean milk and pure food: they taught mothers, nurses, and general practitioners proper care and feeding of infants and children: they organized the service for newborn and sick children in the hospitals.

In each community where a good pediatrician was located, hundreds benefitted for every child he saw as a private patient. The steady progress which has made the children of the United States the healthiest in the world has been the work of these pioneers and missionaries, working as individuals and through their voluntary associations. During this time they have contributed more to the advance of medicine than all other countries of the world combined.

Would this have been true if a paternalistic government had undertaken to furnish all children with health care, as education is provided by our government? I cannot believe that it would. I fear interference with our present freedom of enterprise and endeavor. I believe the most productive expenditure of public funds would be to assist young graduates during years of internship and residencies. Not until more pediatricians are educated will we have better care for more children.

The organization of Region V, comprising the Latin-American countries, is a promising step in our advancement. As you know we were forced to give up plans for a Pan-American congress in 1948. We hope that the Washington meeting arranged by Dr. Hurtado for the members of this region, will speed up its growth and lead to a closer union of the pediatricians of the Western Hemisphere.

I was present at the birth of the Academy, when about a dozen of us met at the home of Dr. James Rosenfeld, during an A.M.A. convention in Portland. We decided the time had come to create a national society of pediatricians. That night, the name "Academy of Pediatrics" was chosen at the suggestion of Dr. Isaac Abt. Dr. Grulee was suggested as secretary, and each of us made a list of ten, who were invited to become charter members. It was my privilege to serve on the first executive board as regional chairman. Now, in my later years, I have come back into its inner councils. I find it has attained maturity. It is a strong, vigorous, "going" concern; the finest

ideals of service have governed its leaders. It has made an outstanding contribution to the development of pediatries. I am very proud to have had a small place in its history.

In reviewing the growth and development of the Academy, I wish to pay tribute to the man who has made the greatest contribution to its success. From the beginning, our secretary, Dr. Grulee, has been the mainspring. Without his assistance and advice, the elected officers would have trod a difficult and uncertain road during their brief terms of office. His conservative yet constructive influence in the Executive Board's direction of affairs, has been a great factor in avoiding mistakes and furthering worth-while undertakings.

There is a project under consideration for the erection of a building to house a library and museum and perhaps the Academy offices. As many of you know, Dr. Grulee has a very large and complete private pediatric library, which he offers to give us. I sincerely hope, that means may be found for the proposed building. No matter what name it is given, to me, it will be a monument to the lifework of Dr. Clifford Grulee.



## DEFICITS IN DIARRHEA

JAMES L. GAMBLE, M.D.

BOSTON, MASS.

THIS paper discusses briefly the development in diarrheal disease of deficits of body water and electrolyte on the one hand and of energy stores on the other, with the purpose of defining features of difference which have relevance to parenteral fluid therapy.

Since water and the electrolytes are not destroyed within the body, they will serve the body as long as the body can hold on to them. This is not the case for the oxidizable food substances which sustain the energy metabolism. It is their destiny to be destroyed; they serve the body only once. Reductions of uptake of water and electrolytes from the gastrointestinal tract will result from increased outgo in the stools and also from lowering of the infant's ability to accept food. The usual intake of water and electrolytes by an infant provides a very large surplus over obligatory outgo in the urine. So we can have large reductions of uptake from the gastro-intestinal tract which will be covered by corresponding limitation of removal of water and electrolytes by the kidney. When, however, the limit of renal conservation is overpassed, deficits will develop with dangerous rapidity. The infant's food provides only the small surplus of oxidizable substances, above the requirement for energy expenditure, which is needed for growth. Even a small reduction of uptake of these substances will, therefore, cause progressive depletion of the energy stores of the body. In other words, in contrast with water and electrolytes, there is no adjustment which will offset reduction of calory uptake. These are quite simple and evident physiologic propositions. The purpose of the following data is to give them quantitative illustration.

The data in Chart 1 are borrowed from a recent unpublished study of water balance in infants by Pratt and Bienvenu (personal communication). The first diagram presents the values found for the components of the water exchange of a 3 kg. infant receiving a food intake composed of a usual dilution of evaporated milk. The intake of water is shown on the left side of the diagram together with the water produced within the body by oxidation of the food substances. On the outgo side we have a relatively small loss of water in the stools and the water which leaves the body by way of the lungs and skin, the so-called insensible water loss, which has an approximately stationary value. Regulation of the remainder of water outgo so as to provide the small positive balance required for growth, shown at the top of the diagram, is performed by the kidney. This water is much more than the kidney needs for excretion of the daily quantity of substances claiming removal in the urine. The measurements recorded in the next diagram of the chart are from a period during which the infant was given

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Borden Award, Fifteenth Annual Meeting of the American Academy of Pediatrics, Pittsburgh, Pa., Feb. 24-27, 1947.

undiluted condensed milk. A normal water balance was found in the presence of reduction of water intake to about one-fourth the usual quantity. There were small reductions of insensible water loss and of water in the stools, but, as the diagrams make quite clear, the large adjustment which preserves water balance is limitation of water outgo by the kidney; urine water is reduced to about one-eighth the quantity found for a usual water intake. These data serve to show the very large water surplus which a usual food intake provides and the extensive conservation of water which can be gained by regulation of outgo in the urine.

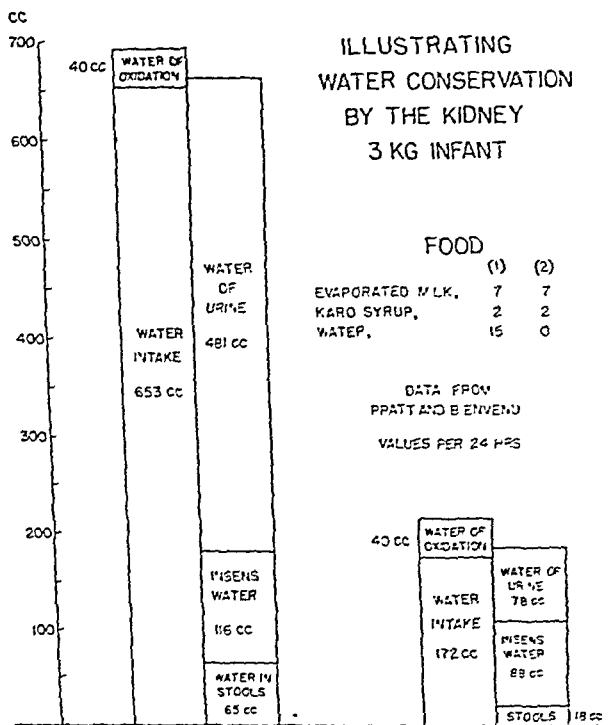


Chart 1.

The diagrams in Chart 2 are constructed from values taken as average for a 7 kg. infant. The first one defines the components of the water exchange with a usual food intake. The small water loss in the stools is placed at the top of the outgo column and the fixed value for the insensible water loss at the bottom. In between is the water removed by the kidney to the extent which provides the small water gain to the body which growth requires. In the next diagram, water expenditure by the kidney has been reduced to its minimal value with the purpose of measuring the extent to which water may be lost in the stools in the presence of a usual intake without disturbing water balance. Very rarely does diarrhea produce a stool volume as large as this. According to the classical study of Holt, Courtney, and Fales, the average value for daily loss of water in the stools of severe diarrhea may be taken



Using the average value found by Holt, Courtney, and Fales\* for sodium in the stools of severe diarrhea, the permissible reduction of intake is found to be somewhat less than for water.

So, according to these diagrams, owing to the kidney's ability to extensively conserve water and sodium, balance may be preserved in severe diarrhea, even when there is considerable reduction of intake. It is evident from the diagrams that, with further reductions of intake, deficits will develop. At the outset of acute severe diarrhea there is extensive, often complete, refusal of food, followed by gradual recovery of intake tolerance. It is evident from the chart that, for a given degree of diarrhea, the requirement for parenteral provision of water and electrolyte will be determined by the extent of reduction of intake.

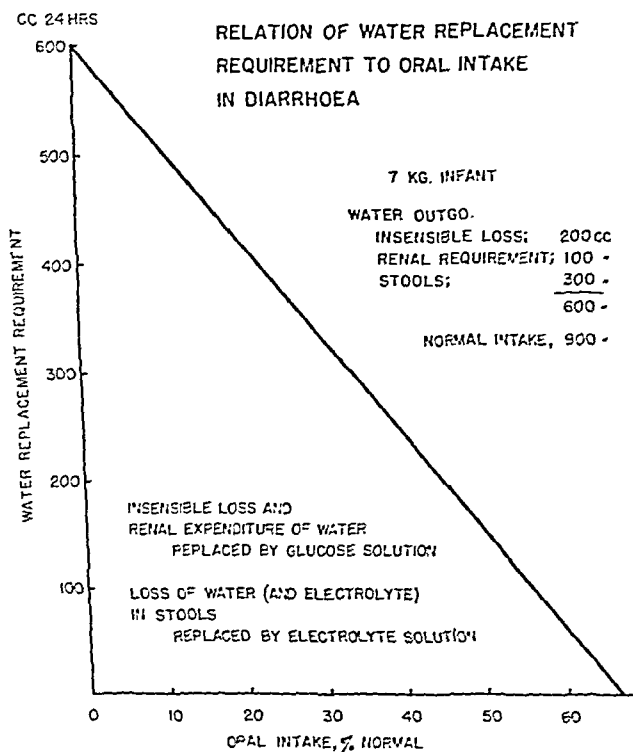


Chart 3.

This is shown in Chart 3, in terms of the water requirement for a 7 kg. infant with a daily stool volume of 300 c.c. and an obligatory water expenditure of 300 c.c. by way of the lungs, skin, and kidneys. So that, with no oral intake, replacement of 600 c.c. of water will be required parenterally. It may be noted here that glucose solution should be used to cover the physiologic expenditures of water, and electrolyte solution to replace the pathologic loss of body water and electrolyte in the stools. When intake is built up to 65 per cent of the usual quantity, this hypothetical infant will not require water parenterally.

\*Holt, L. L., Courtney, A. M., and Fales, H. L.: *Am. J. Dis. Child.* 9: 212, 1915.

as 300 c.c. As shown by the broken line across the diagram, a stool volume of 300 c.c. will not disturb water balance until intake falls below about two-thirds of its usual value.

The other pair of diagrams have to do with sodium. Sodium and its companion extracellular fluid ion, chloride, are particularly exposed to loss in diarrheal stools because they are the two large components of the gastrointestinal secretions. The first diagram displays the enormous surplus of sodium which the infant's food provides in relation to the small daily gain to the body which growth requires. Under normal circumstances, only the small bit of sodium shown at the top of the outgo column is lost in the stools, and so the huge surplus from intake has to be carried into urine. The kidney can limit outgo in the urine to the very small quantity shown in the next diagram.

7 KG INFANT. INTAKE 1000 CC COW'S MILK AND WATER, 3:1

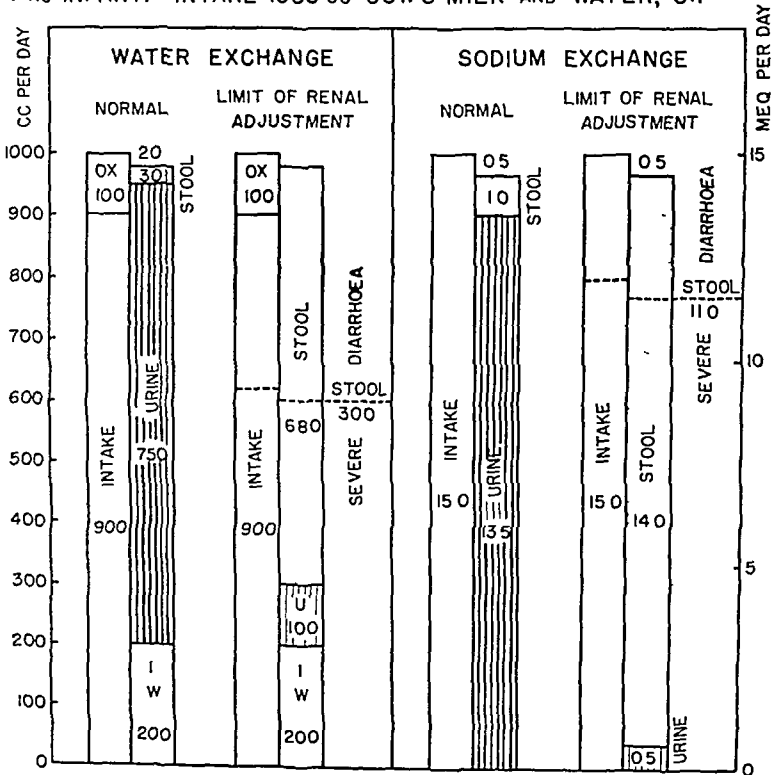


Chart 2.

According to the small values for retention and obligatory outgo in urine shown in the diagram, more than 90 per cent of sodium intake can be lost in the stools without causing deficit. The position of sodium balance is not, however, so secure as these data suggest, for the reason that the loss of sodium in diarrheal stools is relatively somewhat larger than the loss of water.

available from body fat and expendable body water, by the deficits found respectively for energy and water.

As has already been considered, loss of the oxidizable food substances from a usual food intake produces energy deficit, and this deficit will obviously be increased by reduction of the food intake. Energy deficit, then, begins at the outset of diarrhea, but, according to the preceding chart, water deficit will not begin to develop until food intake has been considerably reduced. And so, as shown by the chart, survival in relation to reduction of intake is at first governed by energy deficit. On the basis of a loss of 20 per cent of energy intake in the stools, survival expectancy for a 10 per cent reduction of intake is, according to the chart, 100 days, and falls to fifty days for a 30 per cent reduction. With further reduction of intake, the limit of renal defense of water balance is overpassed and water deficit takes over command and brings survival rapidly down to the desperately narrow margin of three or four days for the situation of complete intake intolerance.

For the long-lasting watery diarrheas produced by persistent parenteral infection and by other causes, the situation is described by the first part of the chart. Limitation of food intake is usually not extensive, so that dehydration is not often a feature of these diarrheas, even when the stools are very large. The infant approaches the edge of existence gradually by way of calory deficit.

An outstanding feature of acute severe diarrhea is extensive, often complete, failure of food acceptance by the infant. By energetic provision of water and electrolytes parenterally we can sustain the body fluids in this situation and bring survival expectancy back to the limit imposed by calory deficit as shown by the broken line on the chart. The broken line tells us that the interval of time within which this infant must be carried through a severe episode of acute diarrhea, by sustaining the body fluids until food intolerance abates and then rebuilding the food intake, is twenty to thirty days.\* Ordinarily, this can be accomplished well within the period of grace, so that we do not have to worry about the progress of calory deficit toward the survival limit. But, unfortunately, we encounter many instances of severe diarrhea, with more or less extensive reduction of intake tolerance, which run a protracted course measured in weeks rather than days. If this chart is anywhere near the mark as an estimation of this situation, the requirement for provision of calories parenterally must be recognized.

How to do this is the most urgent problem in the treatment of diarrhea. More glucose can be provided by using a 10 per cent solution instead of the usual isotonic 5 per cent solution. Infusion of higher concentrations of glucose is, on several counts, undesirable. It would also be desirable to reduce the loss of body protein which is incidental to a sub-energy maintenance intake, which probably limits survival more narrowly than does depletion of the fat stores of the body. Unfortunately, unless the energy requirement is completely covered, the greater part of protein provided parenterally in the form

\*The small contribution to energy incidentally provided by the glucose solution given to sustain the water exchange should extend survival for calory deficit slightly beyond the broken line.

This chart is intended to illustrate the relation of current water deficit to intake. It makes no allowance for body fluid deficit incurred before institution of treatment. This deficit must, of course, be estimated for the individual patient and replaced by additional electrolyte solution.

Chart 4 is intended to display the main features of difference between water deficit and caloric deficit in relation to survival. This is a much more venture-some fantasy from the armchair. The data should be accepted with several grains of electrolyte. We have again our standard 7 kg. infant who voids with preposterous precision a daily stool of 300 c.c. and receives along the abscissa a declining food intake. Estimations of days of survival, based on rates of expenditure of body fat and of body water, are recorded on the ordinate.

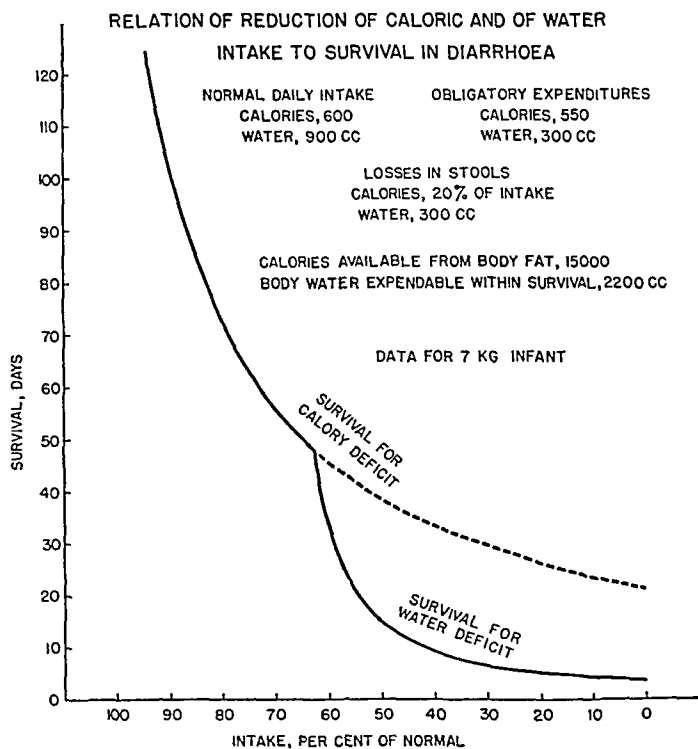


Chart 4.

The infant is assumed to have been well nourished at the outset of diarrhea and to have had fat on deposit in his body to the value of 15,000 calories. It is also assumed that the daily loss of calories in the stools is 20 per cent of the intake. The quantity of body water expendable within survival is taken as 2,200 c.c.\* Estimation of daily deficit at a given reduction of intake is derived from the values on the chart for normal intake, obligatory expenditure, and loss in the stools. Survival is then estimated by dividing the calories

\*Estimated on the basis of maximal losses within survival of 30 per cent of intracellular and 60 per cent of extracellular body water.

## RICKETTSIAL DISEASES OF CHILDHOOD

### A CLINICAL PATHOLOGIC STUDY OF TICK TYPHUS, "ROCKY MOUNTAIN SPOTTED FEVER," AND MURINE TYPHUS, "ENDEMIC TYPHUS"

J. CYRIL PETERSON, M.D., JAMES C. OVERALL, M.D., AND JOHN L. SHAPIRO, M.D.  
NASHVILLE, TENN.

ROCKY Mountain spotted fever and murine or endemic typhus are the important proved rickettsial diseases of children in this country. In recent years, there has been a marked increase in the known area of endemic Rocky Mountain spotted fever. There has also been a marked spread of the areas of endemic infection and a marked increase in the number of cases of murine typhus fever. A number of brilliant epidemiologic studies have appeared, which aid in a definition of the over-all problem of rickettsial disease, but there is a paucity of material concerning the clinical manifestations of Rocky Mountain spotted fever in children and an almost complete absence of clinical studies of murine typhus in children.

In the past fifteen years we have had an opportunity to study twenty-six cases of Rocky Mountain spotted fever, with seven autopsies, and, since 1942, fifteen cases of murine typhus in children. This clinical material, while small in amount, has been studied systematically\* and should enable us to add substantially to the clinical descriptions and to information concerning pathologic physiology of the diseases.

The recent introduction of a satisfactory therapeutic agent for the treatment of rickettsial infections makes such a study timely.

The term "Rocky Mountain spotted fever" has lost most of its significance. The disease is no longer so geographically limited. The inclusion of Sao Paulo fever and Colombian spotted fever with Rocky Mountain spotted fever extends the geographic limits of this disease within the western hemisphere. The term "tick typhus" would seem to be a simpler and a more significant designation for the disease. The word typhus (Greek: *typhos*, meaning cloudy or stuporous) is certainly a descriptive term, more appropriate for this disease than for the milder murine typhus. And, as far as has been determined, some species of tick is invariably responsible for the transmission of the disease. The term tick typhus will be used throughout the remainder of the paper, not only because we think it a more appropriate term, but also because of its desirable brevity.

The endemic typhus fever in this country has been designated by a number of terms, and of these, Brill's disease has real merit from the viewpoint of priority but eponymic nomenclature of disease suffers from descriptive poverty.

From the Departments of Pediatrics and Pathology, Vanderbilt University School of Medicine, Nashville.

Presented before the Fifteenth Annual Meeting of the American Academy of Pediatrics, Pittsburgh, Pa., Feb. 24-27, 1947.

\*The study of these cases was initiated under the guidance of Dr. Katharine Dodd and Dr. Ann Minot. They were cognizant of the significance and importance of the endothelial lesions of the capillary bed and of their relationship to many of the manifestations of these diseases.



of hydrolysates will be oxidized for energy. It is possible to provide a full calory intake by continuous, or almost continuous, infusion of 10 per cent glucose solution. This procedure requires, besides technical experience, constant surveillance by especially skilled nurses, and so is not widely available. It also requires a volume of water which is far beyond the physiologic need.

The great desideratum would seem to be fat in such form that it can be given parenterally, and it is to be hoped that current attempts to produce a preparation of fat which will serve this end will go forward successfully.

foci of relatively high prevalence are recognized. Chart 1 shows the summary of reported cases in the United States for the years 1940 to 1944, inclusive. Fig. 1 shows the numerical prevalence of reported cases in the states for the same period. From this illustration it is apparent that while the major foci of the disease are in the upper South Atlantic states and in the northwestern mountain area, the disease is endemic throughout the United States.

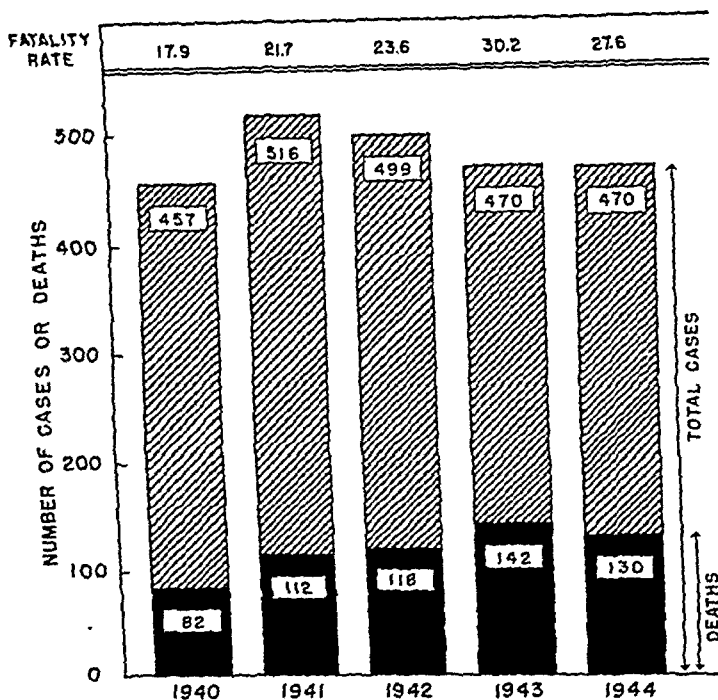


Chart 1.—Number of cases and deaths from tick typhus in the United States from 1940 through 1944.

While it is strongly suspected that tick typhus was occurring in the East prior to 1931, it is not probable that this disease has long been endemic there. It would seem improbable that a disease would be immediately recognized as being different in the West and would remain completely hidden in the East. Nor can this be entirely attributed to confusion with murine typhus, as that disease was not and is not common in many areas where tick typhus has been recognized only in recent years. It is true that most of our patients were seen by physicians and were not correctly diagnosed before they came to the hospital, but some were recognized and many were sent for diagnosis because the physician realized that they were different from infections with which he was familiar.

In Tennessee the study of Litterer<sup>11</sup> makes it seem possible if not probable that the infection was an importation from Montana. Wolbach<sup>8</sup> has pointed out that the disease is not likely to be transported from one area to another by the rodents which serve as reservoir hosts but that it might be transported by larger mammals carrying the tick from one area to another. The establishment of the disease in an area depends upon the presence of satisfactory conditions

Since this typhus has been established as an entity, it would seem best to use a name with more significance than the term endemic, particularly as it is not a disease limited to this country. The term murine typhus, because of its epidemiologic connotation, seems superior to either Brill's disease or endemic typhus. It might even be desirable to call it rat typhus if that would focus public attention upon the necessity of getting rid of rat populations.

#### TICK TYPHUS

Tick typhus is an acute, self-limited, infectious disease of variable severity. The etiologic agent is the *Rickettsia rickettsii*, an obligate intracellular parasite of several species of ticks and of rodents and possibly other mammals. The rickettsia is passed hereditarily from one generation of ticks to another and does not seem to have a deleterious effect upon this host. It is transmitted to man by the bite of the adult tick and occasionally by the bite of nymphal forms. The crushed tick may also serve as a source of infection. The western wood tick, *Dermacentor andersoni*, and the eastern dog tick, *Dermacentor variabilis*, are the principal vectors, but other ticks, *Dermacentor occidentalis*, *Amblyomma americanum*, *Haemophysalis leporis-palustris*, and *Amblyomma cajennense* have been incriminated in the transmission of the disease.

It is fifty years since Woods,<sup>1</sup> an army surgeon, first called to our attention the fact that physicians practicing in southern Idaho had recognized a new disease, a "spotted fever" which was distinguishable from meningococcemia and other known purpuric fevers. This obscure report was quickly followed by the clinical reports of Maxey<sup>2</sup> describing the mild form of the disease as seen in the Snake River Valley in Idaho, and of McCullough<sup>3</sup> describing the severe form of the disease as seen in the Bitter Root Valley in Montana.

These studies were in turn followed by a number of systematic investigations<sup>4-6</sup> into the epidemiology and etiology of the disease which culminated in the work of Ricketts<sup>7</sup> who showed that the disease was caused by a parasite of the wood tick, *D. andersoni*, hereditarily passed from one generation of ticks to another.

Wolbach,<sup>8</sup> in 1919, completely reviewed the previously accumulated information concerning tick typhus, elaborated upon most of the important pathologic features of the disease, and more significantly described the presence of the *R. rickettsii* in the endothelial and smooth muscle cells of the vascular system.

In 1931 Badger, Dyer, and Rumreich<sup>9, 10</sup> demonstrated that tick typhus was not limited to the mountainous section of western United States, but was endemic in the eastern part of the country and that the dog tick, *D. variabilis*, was probably responsible for the transmission of the disease in the eastern United States. They further showed that tick typhus in eastern United States had been confused with murine typhus fever.

Since these studies, there has been widespread recognition of tick typhus throughout the country, cases having been reported from all states but a few in New England. In the five years from 1940 through 1944, cases were reported from every state except Main, Vermont, Rhode Island, and Kansas. Certain

while in the East 47 per cent of the cases occurred in children under 15 years of age. The cases of comparable age distribution show the fatality rates to be quite similar. He showed that the disease is more common in the male in both sections but that the difference is much less in the East, and in children females are affected almost as frequently as males.

While there is little difference in the general severity of the disease when the country as a whole is considered, local differences have been noted since the earliest studies<sup>1, 2</sup> and different strains of the rickettsia produce disease of differing severity in experimental animals.

*Pathology.*—The pathologic lesions of tick typhus provide an excellent background for the interpretation of the clinical manifestations.

A number of excellent studies on the pathology of tick typhus by Anderson,<sup>5</sup> LeCount,<sup>14</sup> Wolbach,<sup>8</sup> Harris,<sup>15</sup> Lillie,<sup>16</sup> Allan and Spitz,<sup>17</sup> and others, have described all of the important pathologic lesions. Many of these studies, however, have been made with scant reference to the clinical manifestations, and in advance of some clinical interpretations. They have consequently emphasized the pathologic histology of the disease in a disproportionate manner.

A brief review of the changes encountered in our cases will serve to orient the reader to our interpretations.

Generally speaking, the most obvious lesion and the one which serves as the most satisfactory locus for the demonstration of rickettsias in tick typhus is the acute arteritis. This lesion has been adequately described by the authors in the foregoing citations. Notwithstanding the attention which has been devoted to this lesion and regardless of its value in the diagnosis of tick typhus, it is not the most important anatomic change in the pathogenesis of the disease. This is most easily appreciated when one considers that the arterial lesions are more prominent in the skin and in the testis than any other organ or tissue and it is obvious that the arterial lesions in these locations can have no fatal consequence, nor could they explain many of the clinical features of the non-fatal disease. If, then, the arterial lesion is responsible for neither the fatal outcome nor the principal clinical features of the disease, some other lesion must be incriminated. Although the lesion to be described has been previously noted, it has been more or less neglected because it is much less spectacular than the arterial lesion. It is much more widely disseminated, however, and is much more significant in explaining the clinical features of the disease. This lesion, a generalized capillary injury, is uniformly encountered in all cases studied, and it adequately explains all of the significant features of the disease.

While capillary damage is found in all of the tissues and organs of the body, it is nevertheless more easily demonstrable and more significant in certain organs. Generally speaking, from the clinical point of view, the principal cause of death seems to lie in the disturbed function of the cardiorespiratory systems. From the pathologic point of view, there is ample evidence to indicate that each of these systems is seriously damaged. The lesion in each is essentially similar and any difference can be explained by the anatomic structure of the

for the propagation of ticks susceptible to infection, susceptible rodents to spread it locally, and larger mammals to carry the infected ticks to different localities.

In the eastern states the infection is transmitted by and is endemic in dog ticks. These ticks may be carried from place to place by dogs and other larger mammals, thereby providing excellent means for the spread of parasitized ticks and also for the spread of the infection to rabbits, the cottontail<sup>12</sup> seemingly being an important factor in the maintenance of the disease.

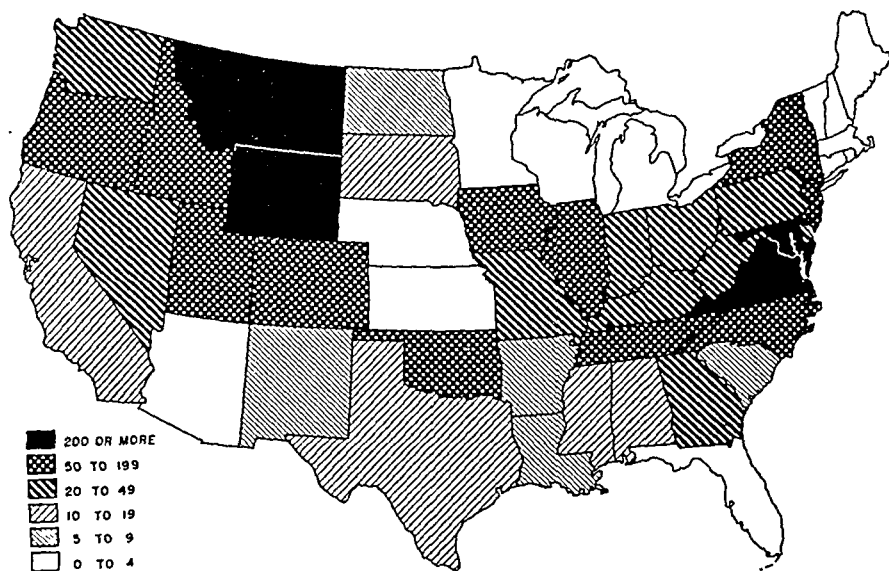


Fig. 1.—Geographic distribution of tick typhus (1940 through 1944).

Tick typhus tends to be a disease of spring and early summer in the West. There the principal vector, the wood tick *D. andersoni*, tends to become dormant with the drought and heat of summer. In the East the cases have a somewhat different seasonal pattern, the principal vector, the dog tick, remains active for a much longer period, and infection is possible the year round but occurs principally in the summer. Twenty-one of our twenty-six patients were seen in the months of June, July, and August. The seasonal distribution is shown in the following table.

TABLE I. SEASONAL DISTRIBUTION OF REPORTED CASES OF TICK TYPHUS

	JAN.	FEB.	MAR.	APR.	MAY	JUNE	JULY	AUG.	SEPT.	OCT.	NOV.	DEC.
U. S., 1940-1944*	12	8	35	166	424	493	529	440	181	66	29	16
Our cases	0	0	0	2	2	5	11	5	2	0	0	0

\*United States Public Health Reports supplements 166, 172, 184, 182, 190. The Notifiable Diseases.

The epidemiologic study of Topping<sup>13</sup> explained certain significant differences which have been noted between the disease in the West and in the East. The higher mortality in the West was found to be due almost wholly to the fact that 50 per cent of all cases there occurred in adults past 40 years of age,

significant and important that the arterial lesions in the heart and in the lungs are very difficult to find. One also finds petechial hemorrhages similar to those which are found throughout the body, but these are of no particular importance.

While alterations in the liver are not as prominent or as important as are those in the heart and lungs, they are, nevertheless, of real significance. The anatomic lesion is characterized by the same capillary damage which has been described before. The localization of the lesion is predominantly in the periphery of the lobule, but there is edema throughout the lobule. Though the intrinsic lesion in the liver is not very impressive, it assumes greater importance when considered in the light of the known function of the liver in the production of plasma protein and especially in the face of the loss of plasma protein because of the widespread capillary damage.

Although Harris has described microscopic infarcts, presumably on the basis of arterial lesions in the brain, we have been unable to find these in any other case. Nevertheless, one finds in the brain the same altered capillary permeability, as indicated by edema and hemorrhage, and it is thought that these can adequately explain the central nervous system manifestations of the disease. These lesions themselves, however, are not usually of sufficient intensity to have any important relationship to the fatal outcome of the disease.

The lesions in the alimentary tract are relatively insignificant in themselves, but it is probable that they interfere with normal alimentation. This may be of especial importance in the digestion and absorption of proteins. Such a disturbance contributes another facet to the complex picture of plasma protein depletion, which is so characteristic in tick typhus.

The lesions in the kidney do not appear to be very significant, but they can adequately explain the mild albuminuria and retention of nonprotein nitrogen encountered in the disease. They are characterized by increased cellularity of the glomeruli and by focal accumulation of inflammatory cells around the thrombosed capillaries of the corticomedullary zone.

The classical cutaneous manifestations are undoubtedly due to arterial lesions, but the widespread edema of the skin and of the body tissues generally must be explained on another basis, and here again the alteration in the capillary permeability is of greatest importance. Anatomic evidence of this damage is detectable in the skin and it resembles in all respects the lesions described in other organs.

While the organs and tissues already discussed appear to be those most significantly and seriously injured, the lesions are by no means restricted to these, for the adrenals, testis, pancreas, and almost every other organ and tissue is similarly involved.

There is one other lesion which at the moment is only of academic interest. This is the characteristic phagocytosis of red blood cells, especially by the reticuloendothelial cells of liver and spleen, but in other organs as well. This erythrophagia is of such a degree that it might well contribute to the anemia which is encountered in some of these patients.

*Clinical Manifestations.*—The onset of the disease is usually abrupt after an incubation period of from two to thirteen days. In two persons purposefully

tissue involved. The essential lesion is an alteration in the capillary bed which is characterized by edema, the accumulation of mononuclear, inflammatory cells, and occasionally by fibrin thrombi in the capillaries.

In the heart this is associated with focal destruction of myocardial fibers and an accompanying mononuclear leucocytic infiltration. These changes are shown in Fig. 2.

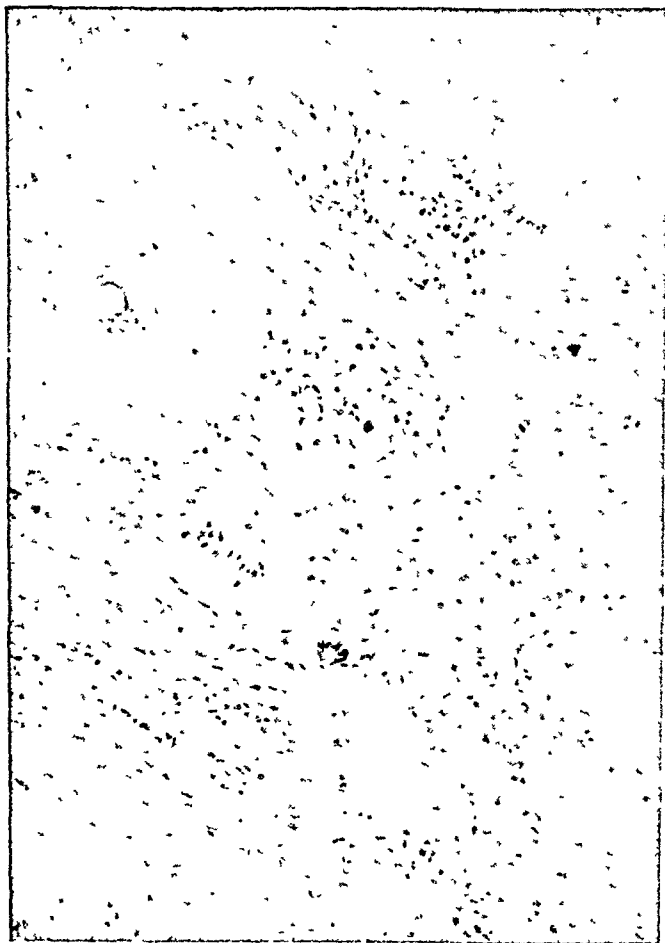


Fig. 2.—The myocardial changes resulting from tick typhus.

In the lungs, the process is recognized as acute interstitial pneumonia, the principal feature of which is serous exudate in the alveolar spaces; but in addition to this one finds mononuclear infiltration of the alveolar walls and, to a lesser extent, the spaces.

The concurrence of these lesions in the heart and in the lungs is so significant that it should allow one to make a tentative pathologic diagnosis of rickettsial disease of the severer type, either scrub typhus or tick typhus. It is

to have been overlooked in the seriously ill, stuporous patient even if spinal fluid showed marked changes from meningeal inflammation. The stiffness of the back and neck was seen, however, in patients who did not have spinal fluid changes on admission and was a prominent symptom in some who died early in the disease.

Several of our patients were brought in with the complaint of swelling, generalized edema, and in one instance this was the chief complaint in that the patient was unable to open his eyes.

Symptoms referable to the respiratory tract were not common, though two patients had signs of pneumonia at the time of admission.

Many patients were treated for several days with quinine in the belief that they had malaria. This was invariably in the stage before the appearance of the rash. Typhoid fever did not enter into the early errors in diagnosis.

As all except one patient had a rash when brought to the hospital, it is not surprising that almost all were correctly diagnosed at admission. The exceptions were the first patient, who was seen in 1931, only four months after the announcement of Badger and Rumreich that the tick typhus had been found in patients in the eastern United States; and a patient without a rash but with an infected foot wound and meningismus which led everyone to suspect atypical tetanus. His rash appeared late on the day of admission, the fifth of the disease, and he died the following morning. The correct diagnosis was made only when the tissues were examined microscopically.

The physical findings at the end of the first week and early in the second week, when the patients came to the hospital, were very typical but were quite limited. On inspection they were all obviously quite ill.

The milder cases were so apathetic that one had to be forceful to arouse their attention and the more severe cases were in semicoma to complete coma. Their facies, which are well illustrated by the photographs, are typical enough to be diagnostic. They show a general clouding of the sensorium just short of that usually seen in acute encephalitis. This finding is undoubtedly due to the widespread involvement of the cerebral vascular system. It is present as early in the disease as the appearance of the rash, in some instances before the rash is apparent, and reaches its maximum degree at the end of the second week or during the third week in the more protracted cases. In the least severely ill patients the typhus state persists only until the fever begins to break but in the most severely ill it may persist well into convalescence. Undoubtedly some patients never recover completely from this encephalopathy. The last patient of our experience, 120 days after the onset, still has marked encephalopathy, central blindness, and central deafness, together with slight but definite hemiparesis. She has just learned to sit up again and has not regained any power of speech. In Fig. 3 is shown the facies of a patient with severe tick typhus four days after his temperature had returned to normal. Three weeks later he was talking with some slight degree of spontaneity but was still mildly ataxic. These severe degrees of encephalopathy are fortunately exceptional. It is interesting that there were convulsive seizures in only one of our patients in spite of the



infected by McCalla<sup>18</sup> by a tick taken from a person with the disease, the incubation period was three days in one and nine days in the other. In our material the incubation period varied from three to ten days in the fourteen patients where a definite bite or contact could be determined. In two patients there was no definite contact with ticks; in two others no ticks were removed but bites were noted the day before the onset; in four patients the ticks were still attached when they were first seen at the hospital. One patient was unsuspected and the question of tick bite was never raised; three were associated with simple handling of the ticks in removing them from dogs (in two of these the tick was squeezed between the fingernails). In one instance the time of removal of the tick was not recalled and in one instance the only known contact was three weeks before the onset. The incubation period in the fourteen known intervals is shown in Table II.

TABLE II. INCUBATION PERIOD IN TICK TYPHUS

Day after bite	3	4	5	6	7	8	9	10
No. cases	4	1	2	1	3	1	-	3

The first complaint in almost every case was severe, unlocalized headache; this persisted as the outstanding symptom until the patients became too stuporous to complain. Aching pains were noted in twelve instances but they were never referred directly to the joints and were often generalized. Anorexia with refusal of almost all foods was usual. There was occasional abdominal discomfort. There was vomiting at the onset in six instances and diarrhea twice as the only other gastrointestinal manifestations. In one-fourth of the patients there were chilly sensations but none of them had frank shaking chills.

The rash was the symptom most likely to alarm the parents and appeared first as a few scattered red macules. The rash usually appeared on the extremities first but this was far from being regular. In the most severe cases the rash began to show petechial hemorrhage into the macule very early but in the milder cases the purpuric quality of the rash first appeared after a period of several days to as long as a week. The rash appeared in less than forty-eight hours after the onset in thirteen instances, in four during the first twenty-four hours, and in several others very early on the second day.

The time of the appearance of the rash and whether it appeared first on the trunk or on the extremities in twenty-six patients seen during the active disease is shown in Table III.

TABLE III. THE TIME AND SITE OF FIRST APPEARANCE OF THE RASH IN TICK TYPHUS

WHERE RASH WAS FIRST SEEN	DAYS OF ILLNESS						TOTAL
	1	2	3	4	5	6	
Extremities	4	7	1	3	1	0	16
Trunk	0	2	2	3	1	1	9
Total	4	9	3	6	2	1	25*

\*In the one Negro patient, the rash was not noted prior to admission.

Another pertinent complaint of these patients, especially those seen in the second week of their illness, was stiffness of the neck and back. This was likely

to have been overlooked in the seriously ill, stuporous patient even if spinal fluid showed marked changes from meningeal inflammation. The stiffness of the back and neck was seen, however, in patients who did not have spinal fluid changes on admission and was a prominent symptom in some who died early in the disease.

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fact that meningoencephalitis was commonly demonstrated both clinically and by spinal fluid changes (see below).

All of our patients showed a slight-to-moderate, generalized edema. Their faces were moon-shaped and the folds about the eyes, wrists, and ankles were obliterated. In the very mildest cases findings were minimal; in the moderate and severe cases they were quite obvious, and in two instances the eyes were swollen shut at some time in the course. This edema appeared as early in the disease as we saw the patients. This is in contrast to five adults whom we have seen with the disease; they, with one exception, were free from easily perceptible



Fig. 3.—Encephalopathic facies and skin pigmentation seen in patients with tick typhus.

edema. The edema is not easily pitted. As seen in the photographs it is generalized and involves both the cutaneous and subcutaneous tissues. This edema fluid is rich in protein, as is easily demonstrated in pathologic sections, and is, no doubt, due to the generalized damage to capillary endothelium. That the loss of protein in this manner is important is shown by the fact that the plasma proteins were regularly reduced but not sufficiently to have been a factor in the development of the edema. In some instances the edema may also have been in part due to cardiac failure but in the main it was the result of the capillary damage.

The rash was the principal general physical finding. Its character is well illustrated in the colored photographs.\* The rash appears first as discrete red

\*The authors were able to publish this plate through the courtesy and generosity of Wyeth Incorporated, who also supplied the para-aminobenzoic acid used in the treatment of some of the patients.



Fig. 1—TICK TYPHUS  
The exanthem, facies and  
generalized edema, especially of the eyelids, as  
seen in the first week.





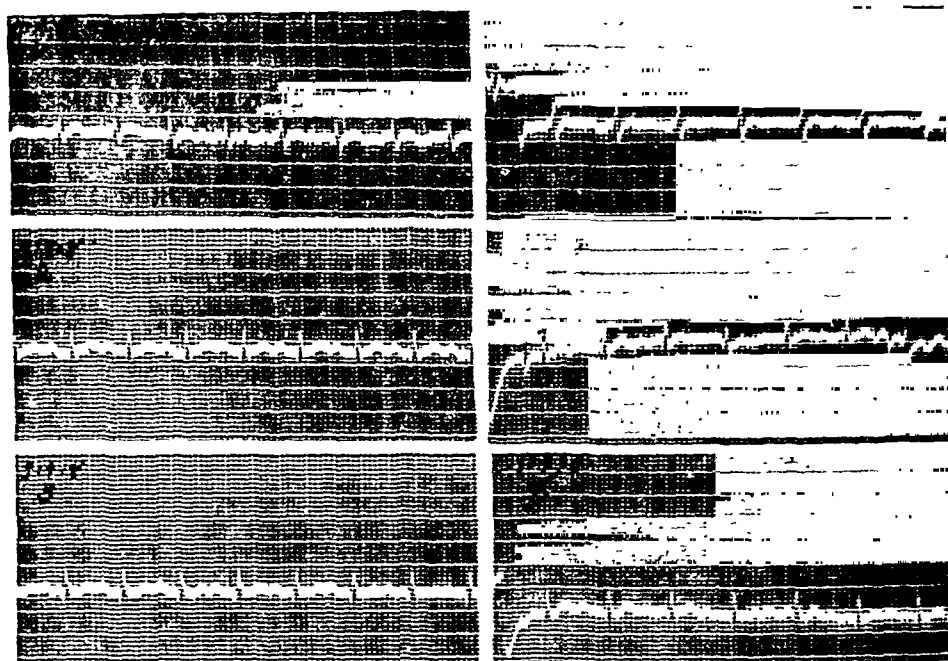
macules which blanch incompletely on pressure. They may appear first on any part but most frequently on the extremities (see Table III). Regardless of where the rash first appears, it soon becomes much more marked on the extremities and involves the palms of the hands and soles of the feet. In all but the mildest cases, the rash, after a period of two to three days, begins to show purpuric manifestations, becomes more intensely red, and fades little if any on pressure. The rash may show petechial hemorrhages or even become wholly purpuric in character. In the most severe cases the petechiae are present in the lesions from the beginning. These are difficult at times to differentiate from the petechiae of meningococcemia. As a rule, however, there is more associated erythema with the lesions of tick typhus.

The rash persists until the patient begins to show signs of improvement, but may begin to fade several days before the lysis of the fever begins. The fading rash leaves a distinct pigmentation of the skin, most marked on the patients who had the severest purpuric manifestations. The character of this pigmentation is apparent in Fig. 3. In the severely purpuric patients the pigmentation may persist for ten days to three weeks before disappearing.

In addition to the above general findings, several other physical changes occur. In all but one of our patients there was a tachycardia higher than one would expect from the observed fever alone. Pulse rates of 140 to 160 were seen, with temperatures of 102° to 104° F. This tachycardia was not infrequently associated with poor quality of cardiac sounds and gallop rhythm. Where these findings were marked there was also distention and tenderness of the liver; but we did not demonstrate clearcut signs of pulmonary congestion by physical examination. Chest roentgenograms usually showed considerable increase in the bronchovascular markings and sometimes slight dilatation of the heart. Electrocardiograms much more regularly showed distinct evidence of myocardial damage. There was marked lowering of the voltage. There was slurring of QRS complex, low voltage  $T_2$  curves, and alterations in the S-T segment. These changes are illustrated by the tracings shown in Figs. 4 and 5. In some of our patients the myocardial lesion was an important contributory factor in their death. In association with these cardiac changes there was usually slight hypotension, blood pressure observations were as a rule not greater than 100/50, and 90/50 was a more frequent observation.

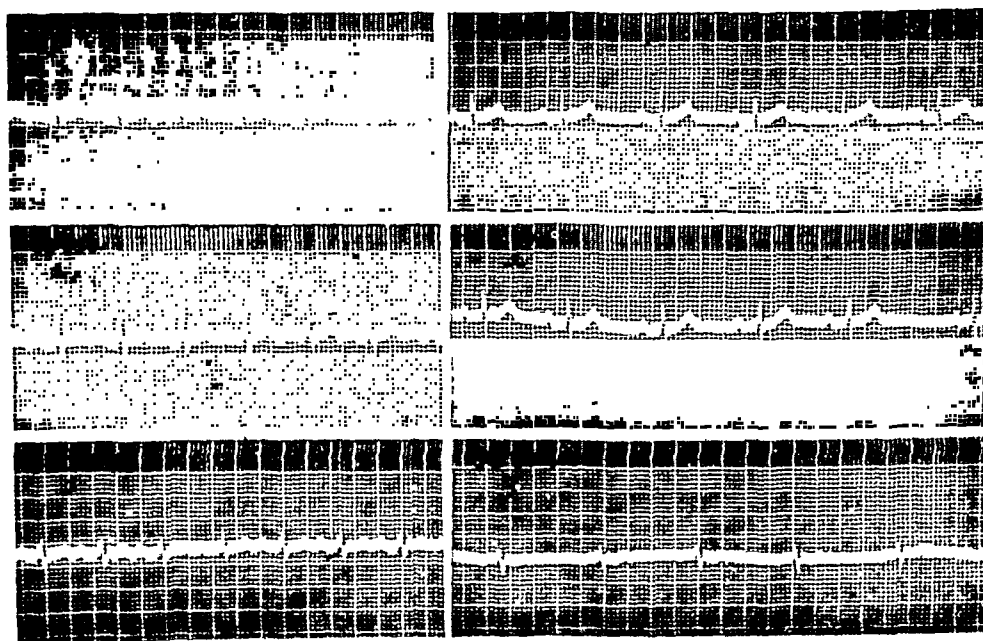
The reasons for the cardiac changes are found in the pathologic studies which show a moderate to severe diffuse interstitial myocarditis (see Fig. 2). Also, the extensive lesions of the pulmonary vascular bed serve as important contributing factors in the cardiorespiratory disturbance. In other patients, shock resulting from the loss of fluid and protein from the vascular bed, hemoconcentration, and depletion of the circulating blood served to further augment the anoxemia and to establish a cyclic state of progressive cardiorespiratory failure.

The lungs, while they were affected by an interstitial bronchopneumonia in some of our patients, rarely showed good clinical signs of this change ex-



13th DAY PRE-DIGITALIZATION    16th DAY POST-DIGITALIZATION

Fig. 4.—Electrocardiographic changes during tick typhus.



12th DAY PRE-DIGITALIZATION    24th DAY POST-DIGITALIZATION

Fig. 5.—Electrocardiographic changes during tick typhus.

cept as a terminal manifestation. Increased and progressive hyperpnea was noted in all of the fatal cases and in some of the patients with severe cases who recovered. Frank decrease in resonance and in the volume of the respiratory murmur with associated râles was found in only two patients at the time of admission; both were fatal cases. The chest roentgenograms as noted above showed only increased bronchovascular markings, and never frank pneumonic consolidation.

The liver as already noted was enlarged in association with myocardial failure but was often not palpable in mild and moderately severe cases. The spleen was palpably enlarged 1.5 to 3 cm. below the costal margin in about half of the patients. There seemed to be no regular explanation for the presence or absence of splenomegaly. This splenic enlargement in the absence of other physical findings in the pre-eruptive phase frequently led to the treatment of the patient for malaria; the quinine, which was usually used, did not modify the course of the infection.

General and local glandular enlargement was noted in about half of our patients, but the significance of this finding in relation to the disease was not apparent.

The freedom from complaints referable to the upper respiratory tract was commented upon above. Only one patient showed catarrhal otitis media and usually the nose and pharynx were clear except for dryness in some instances from the mouth breathing and poor mouth care prior to admission.

Other findings of note were observed in the laboratory studies.

*Clinical Pathologic Data.*—The urine was, as a rule, normal, though in three or four of our patients there were transiently traces of albumin and a slight increase in red blood cells. These were not more marked than one would have expected to find in any group ill with other fevers of a similar degree of severity.

Some of our patients showed moderate degrees of nonprotein nitrogen retention. Transient elevations of 35 to 50 mg. of nonprotein nitrogen were observed in six of eight patients examined during the fifth to tenth day of the illness. Nine other patients observed after the tenth day showed levels of less than 32 mg. Only two patients showed an elevation of nonprotein nitrogen beyond the tenth day, one was a fatal case with myocardial failure, and the other also had severe myocarditis and cardiac failure. The elevations were greatest in the fatal cases and the three such cases in whom observations were obtained showed 47, 48, and 50 mg. per 100 c.c. of blood. The renal lesions in these patients were not more severe than in other fatal cases and consisted of thrombosis of arterioles in the medullary portions with infiltration of the large mononuclear cells and polymorphonuclear cells. There was also some tubular epithelial desquamation with resultant plugging of the tubules. As noted above, renal disturbances as reflected in the urine were conspicuously minimal even in those having a fatal termination. The three patients noted above who showed the greatest nonprotein nitrogen retention had only a 1+ albuminuria.



The disease, because of its short duration, was not associated with marked changes in the red blood cells or hemoglobin at the time of admission. However, it is interesting to note that there were no observations of hemoglobins greater than 14 Gm. or polycythemia (red blood cells above five million) in spite of the fact that many of the patients were suffering from lowering of their blood volume as shown by precipitous drops in the red cell counts and hemoglobins which followed within two or three days upon the re-establishment of adequate fluid intake and the administration of parenteral crystalloid and protein solutions. Many of our patients required blood transfusions during the course of their illness because of the fall in the blood counts and the hemoglobin in addition to the value that such therapy had at times in establishing more adequate blood volumes. The anemia which developed was not different from other secondary anemias.

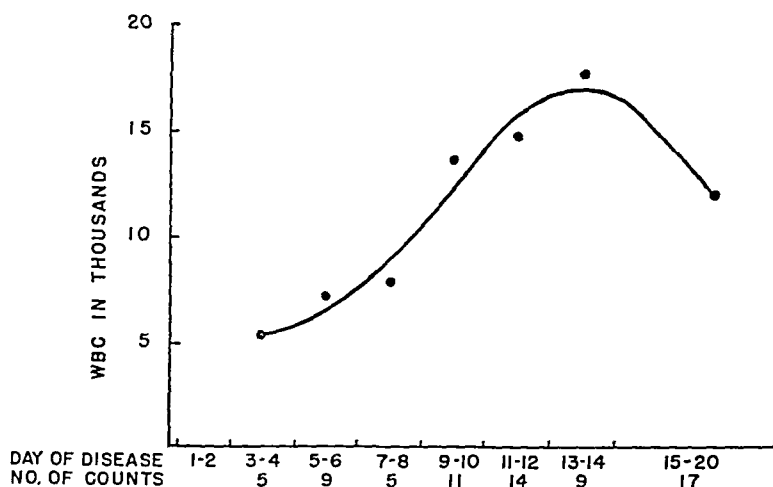


Chart 2.—The white blood cell response in tick typhus according to the day of disease.

The white blood count varied considerably, depending upon the severity of the disease and the stage at which the count was made. Sixty observations were made on our patients and the results are shown in Chart 2.

It is generally stated in textbooks and other clinical descriptions of tick typhus that there is a leucocytosis. Our studies show that during the first week of the disease there is a relative leucopenia. Our counts in the first five days varied from 4,000 to 10,000, with the more severe cases showing the greatest leucopenia. At the end of the first week there is a sharp rise in the white count to average values of 13,700 on the ninth and tenth days, reaching a maximum of 17,800 on the thirteenth and fourteenth days. This leucocytosis falls off sharply after the second week. There was throughout the course a definite polymorphonuclear preponderance, this cell comprising 78 per cent to 90 per cent of the circulating leucocytes, with considerable numbers of stab cells and juvenile cells

being seen even in leucopenic counts. In several instances an increase in the total count on the sixth to seventh day was associated with a fatal outcome but the number of counts involved in our study is too small for this to be accepted as more than a suggestion as to the prognosis. The basic pattern of leucocytic response outlined is similar to that observed by Stuart and Pullem<sup>19</sup> in murine typhus and by Cooke<sup>20</sup> in his report on tick typhus.

Another finding of interest was the change noted in the plasma proteins. A total of twenty-six observations were made at varying stages throughout the course of the disease in nineteen patients. In Table IV is shown the observed values. From these it is apparent that there is a regular lowering of the protein levels and that the albumin-globulin ratio was considerably less than 2:1. These changes are more readily visualized in Chart 3, where the observed values for different periods are averaged and plotted. By the fifth and sixth day, the time of our earliest observations, there was already a lowering of the proteins to nearly the ebb level. After the twelfth day, the observed values were higher but the increase was almost wholly in the globulin fraction, and after the sixteenth day, the observed values for globulin were as high or higher than the al-

TABLE IV. PLASMA PROTEIN IN TICK TYPHUS

CASE NO.	DAY OF DISEASE	TOTAL SERUM PROTEIN	ALBUMIN	GLOBULIN
8	5	5.7	3.7	2.0
9	6	4.1	2.2	1.9
10	6	4.9	2.5	2.4
13	6	6.2	3.8	2.4
13	10	5.8	3.5	2.3
13	16	6.5	3.5	3.0
5	7	4.6	3.0	1.6
5	11	4.9	2.8	2.1
5	13	6.0	3.6	2.4
15	8	4.8	2.7	2.1
17	8	6.2	3.8	2.4
18	8	5.5	3.2	2.3
18	12	5.5	2.9	2.6
11	9	5.0	3.0	2.0
16	9	5.1	3.4	1.7
16	15	5.4	2.9	2.5
19	9	4.7	2.7	2.0
19	13	6.0	3.5	2.5
7	11	5.3	3.1	2.2
12	11	4.7	2.6	2.1
12	18	5.8	2.6	3.2
12	21	7.0	3.4	3.6
12	23	6.9	3.9	3.0
14	11	4.7	2.4	2.3
14	18	5.7	3.2	2.5
22	11	4.1	2.4	1.7
22	14	4.2	2.5	1.7
22	16	4.9	2.9	2.0
22	22	5.6	2.8	2.8
21	12	3.9	2.4	1.5
6	16	5.9	3.3	2.5
20	15	5.9	3.1	2.8
25	15	5.7	3.2	2.5
25	16	5.8	3.2	2.6
25	18	7.2	3.6	3.6

bumin values with a ratio of about 1:1. That individual patients follow a similar pattern is shown in Chart 4, where the cases having multiple observations are shown.

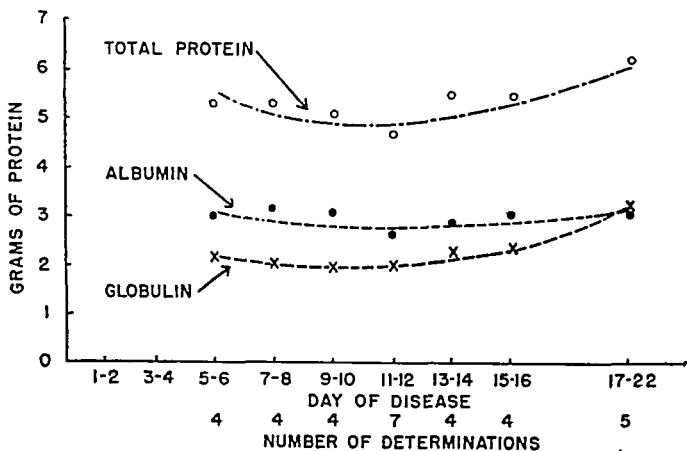


Chart 3.—Serum proteins during the course of tick typhus.

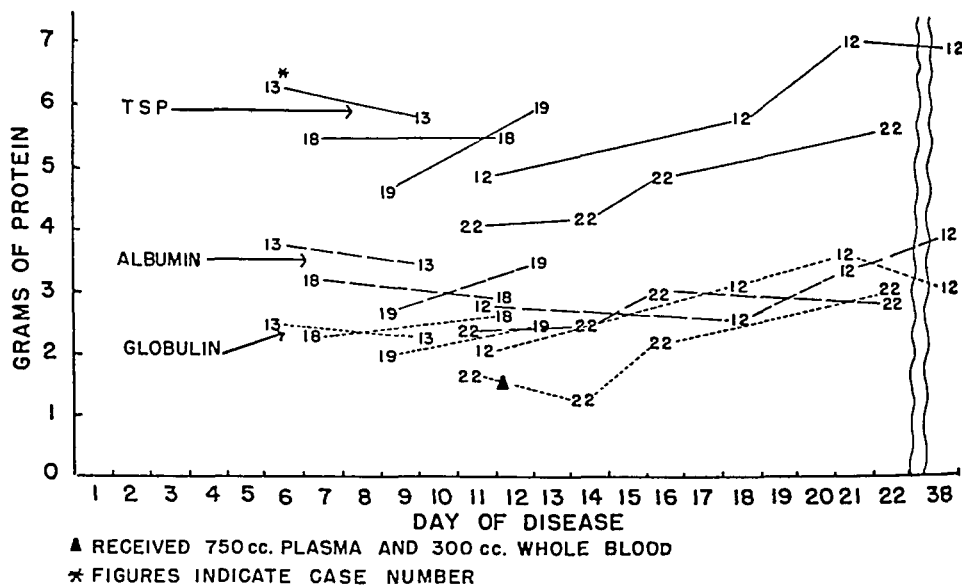


Chart 4.—Individual serum protein variations in the course of tick typhus.

It seems apparent that these changes in the plasma proteins are related in a considerable degree to the increased permeability of the vascular bed and to the loss of protein into the tissues. That this is not the only factor involved, however has been shown by the studies of Harrell<sup>21</sup> and his associates, who have

shown that this plasma protein depletion can be minimized by a very high protein intake. The liver injury probably also contributes importantly to this difficulty in maintaining the plasma proteins.

The encephalomeningitis noted on physical examination was reflected in the changes observed in the spinal fluid. Thirty-six observations were made on twenty-four of the patients. Two-thirds (twenty-five) of the observations showed moderate degrees of pleocytosis. Of the eleven counts showing normal values of less than 5 cells, six were in patients in whom another observation, later or in one case earlier, showed definite pleocytosis; one was in a patient treated early and successfully with para-aminobenzoic acid; two were on patient Number 1 on consecutive days (this child, two days later at necropsy examination, showed marked meningeal changes); the others were single observations on patients on the fifth and eighth day. The scatter of these observations is shown in Chart 5.

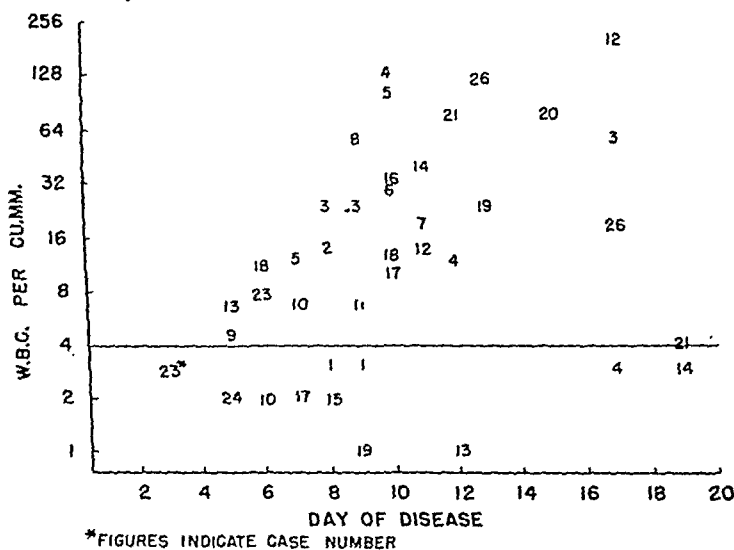


Chart 5.—Spinal fluid pleocytosis in tick typhus.

The character of the cellular response varied considerably; usually most of the cells were lymphocytes, but occasionally in slightly elevated counts early in the course of the disease there was a preponderance of polymorphonuclear cells. The maximum cell count was 182 in a very severe but nonfatal case on the seventeenth day. The cellular response was usually associated with an increase in protein, usually 1+ or 2+ positive Pandy tests. In eight instances where the spinal fluid proteins were observed quantitatively, the response varied from 30 to 189 mg. with an average value of 79 mg. Quantitative sugars were observed more frequently and were usually thought to be normal on simple estimation. The sugar levels varied from 48 to 76 with an average of 58 mg. per 100 c.c.

It is apparent from this study that there is regularly a spinal fluid pleocytosis and increase in the protein. In respect to the cerebral involvement, tick typhus is more like epidemic typhus than is murine typhus.

Our patients were all examined for their antibody response to the infection as measured by proteus OX<sub>19</sub> agglutinations and some by agglutinations versus proteus OX<sub>2</sub> and OX<sub>k</sub> and in later years for the development of complement fixing antibodies against *Rickettsii* and *R. mooseri*.

Two proteus agglutinations done in our own laboratories, the Tennessee State Department of Health Laboratories, and the National Institute of Health Laboratories, have shown considerable variations in the degree of response and as to whether the titer was greatest against one proteus variant or another. This test usually becomes positive by the eighth to tenth day, but occasionally not until the end of the second week. It is probable that the immunologic immaturity of our patients is responsible for this delay as contrasted to the appearance of these agglutinins in adults. The test is useful in establishing the diagnosis of rickettsial infection, but is nonspecific. No combination of proteus agglutinations can serve satisfactorily to establish the identity of a rickettsial infection.

The response with complement fixing antibody occurs later than the proteus agglutination. Again, tests run in different laboratories have shown some variation, chiefly in the titer but also as to specificity. In the earlier tests there was sometimes response to both *R. rickettsii* and to *R. mooseri*. With the improvement in the rickettsial antigens by Plotz and his group,<sup>51</sup> this lack of specificity has disappeared, and at present laboratories usually report little or no crossing of the complement fixation tests. While our material is too small to be worth more detailed analysis, we can with justification say that the complement fixation test is now, in the hands of qualified laboratories,\* an adequate and reliable means of establishing the identity of the rickettsial infections. Two samples, one on the fourteenth to seventeenth day of the disease and another on the twenty-first to twenty-fourth day, should invariably yield information to make a satisfactory diagnosis.

*Clinical Course.*—The cases of tick typhus seem to be devisable into a mild and a severe group and the different groups almost can be separated from the beginning of the infection. Cases 2 to 8 in our group were of the mild group, and we were convinced that the disease was almost always fairly benign in children, but Cases 9 to 16 were of the more severe group and there were four fatalities in the eight cases.

This group of serious cases also came at a time when it was thought that parenteral fluids would overwhelm the circulation, and the patients were not given the benefit of adequate treatment for their circulatory failure. None of the patients with fatal cases lived as long as forty-eight hours after admission to the hospital, and all may be classed as malignant. Two of them died on the sixth day of the disease and two on the tenth day. Of the other fatalities, one

\*Tests for complement fixation have been run for us through the courtesy of the laboratories of the Tennessee State Department of Health, the United States Public Health Service Laboratories, and the Virus and Rickettsial Laboratories of the United States Army.

was our first patient, who died on the thirteenth day of her illness with cardiac failure and an overwhelming involvement of the central nervous system; another was our nineteenth patient, who died after ninety-six hours' hospitalization on the thirteenth day of her illness with cardiac failure and widespread pneumonitis; and the seventh was our twenty-fourth patient, who died on the fifth day of her illness, less than twenty-four hours after admission, from a malignant infection. Cardiac failure and pneumonia were obviously present as terminal events. With modern therapy the fatality rate could undoubtedly have been lowered and in some of the patients more vigorous supportive therapy, particularly relating to the prevention of shock and cardiac respiratory failure, might have turned the course of the infection.

In the mild and moderate cases, the patients ran a favorable course from the beginning. The rash was slow to develop purpuric characteristics; the fever as a rule was not more than 104° F.; the patients were stuporous and apathetic but could be easily roused; they took food fairly well and maintained an adequate fluid intake without recourse to parenteral administration; they showed no evidence of myocardial failure and did not tend to develop shock. Most of them began to show improvement in their reactions before the end of the second week of the illness and the fever fell by lysis to normal at an earlier date. The duration of the illness in the mild and in the severe but nonfatal cases, is shown in Table V.

TABLE V. DURATION OF FEVER IN TICK TYPHUS IN SURVIVING PATIENTS

	DAY ON WHICH TEMPERATURE REMAINED LESS THAN 100° F.												
	UNDER 10	10	11	12	13	14	15	16	17	18	19	20	21 OVER 21
Mild cases	1*†	-	-	-	1	-	1	3	-	6	1	-	-
Severe cases	-	-	-	-	-	-	1†	-	-	-	1	1	2‡

\*Eighth day.

†Treated with para-aminobenzoic acid.

‡Twenty-fourth and twenty-sixth days.

The surviving severe cases were distinguished from the mild by their duration as well as by their general course, the fever persisting to the end of the third week and even well into the fourth week. Case 25, whose temperature was normal on the fifteenth day, was the only severe case terminating before the nineteenth day. This early termination was thought to be due to treatment.

*Diagnosis.*—The diagnosis of tick typhus in the pre-eruptive phase may always be a practical impossibility though a presumptive diagnosis can be made in some cases where one finds an engorged tick attached to the patient or obtains a history of the recent removal, or the handling and particularly the crushing of a tick. Cases of obscure fever occurring in the late spring and early summer in endemic areas should be considered with a high index of suspicion. The sudden onset, the headache, generalized aching pains, and the leucopenic or normal white blood count should serve to call attention to the possibility of tick typhus. The sudden onset should serve to exclude typhoid fevers and variable splenomegaly and freedom from remission should aid in ruling out malaria. In many endemic areas the question of malaria will not enter into the differential diagnosis.

The appearance of the rash will, in almost every case, allow one to make a reasonably certain presumptive diagnosis. The diseases most likely to be confusing are meningococcal sepsis and murine typhus. Meningococcal infections will, as a rule, be differentiated by the associated purulent meningitis, the leucocytosis, and the cultural identification of the organism. Murine typhus on the other hand will be differentiated as a rule by the clinical course, being a much milder disease. The rash in murine typhus is most intense over the trunk, while a peripheral distribution is characteristic in tick typhus. The rash of murine typhus is rarely purpuric, while that of tick typhus is almost always purpuric when fully developed. There will undoubtedly be some cases which can be differentiated only upon the basis of specific laboratory tests.

While it is not the province of this paper to discuss the technique of these laboratory studies, their uses should be enumerated. The rickettsias may be isolated from patients by inoculation of guinea pigs with blood from patients with either rickettsial disease. The animals may become sick with characteristic illness, with or without scrotal lesions.

More practical from the clinician's viewpoint is the differentiation on the basis of serologic study. As mentioned before, the agglutination of proteus OX<sub>19</sub> serves to establish the infection as a rickettsial disease, and complement fixation studies with specific rickettsial antigens serve to differentiate the rickettsial infection. The uses of these tests were discussed under the section on laboratory findings.

*Treatment.*—The treatment of patients ill with tick typhus may be divided into two phases, the specific attack on the infection and the general measures needed to combat the profound physiologic disturbances encountered.

Two methods are available for the specific treatment of tick typhus. The first of these was introduced by Topping<sup>22</sup> and is a specific antiserum. To date this serum is available only for experimental observations, but the reports of Topping<sup>22</sup> and Harrell and associates<sup>21</sup> indicate that serotherapy has encouraging possibilities.

The studies of Topping<sup>22</sup> show that serum therapy to be fully effective must be started in the first three days of the rash. He reported the results in the treatment of seventy-one patients, fifty-two of whom received treatment before the third day of the rash and nineteen of whom were treated later. The mortality for the group as a whole was exceptionally low (5.6: the over-all mortality had been shown to be 23.4). Not only was there an improvement in mortality as a whole, but there were fifteen patients in the early treatment group whose fever persisted longer than twenty days, indicating a high proportion of what may be looked upon as severe infections. It should also be pointed out that while both groups were treated, those receiving treatment early showed an average duration of fever of seventeen days, while those receiving delayed treatment had an average duration of twenty days, in spite of the fact that the latter group contained a high proportion of young individuals who are recognized as having a better capacity to respond to the infection. Harrell<sup>21</sup> and his group noted that there was no apparent edema in the individuals who received serum therapy,

thus suggesting that this form of therapy is effective in preventing or at least ameliorating vascular damage. It should be pointed out that the treatment consisted of a single injection of antiserum without any assurance that an adequate or optimal amount was being administered. These studies need extension and repetition. They also emphasize the need for an improvement in diagnosis which will permit earlier treatment.

The second specific therapy for tick typhus is chemotherapy with para-aminobenzoic acid (paba) or sodium paba.\* The possibility of using this agent in rickettsial therapeutics was first suggested by Snyder and associates.<sup>23</sup> Hamilton and associates<sup>24</sup> and independently, Grieff and associates<sup>25</sup> showed that paba was effective in preventing the growth of rickettsias in embryo cultures. The studies of Yeomans, Snyder, Murray, Zarafonitis, and Eke<sup>26</sup> showed that paba was effective in experimental rickettsial diseases and in louse-borne typhus. Anigstein and Bader<sup>27</sup> showed that it was effective in experimental tick typhus. These studies have been followed by several clinical reports showing that paba is effective in treating various rickettsial diseases.

Rose and his associates<sup>28</sup> reported an excellent response to treatment with paba in a severe or moderately severe case of tick typhus. The response was apparent from the precipitous drop in fever on the third day of treatment.

Tierney's study<sup>29</sup> revealed that effective therapy with paba required blood levels of 30 to 60 mg. per 100 c.c., and that such levels could be obtained in adults when 8 Gm. of paba were given as an initial dose followed by 3 Gm. every two hours. In the serious rickettsial disease, scrub typhus, this regime was strikingly effective in the lessening of severe symptoms and complications and in cutting the average duration of the febrile course from twenty to ten days.

In Smith's study<sup>30</sup> of the effect of paba in murine typhus, a smaller dose of drug was used and less dramatic results were obtained. He used 2 Gm. every two hours and did not observe the blood levels obtained. He did obtain shortening of the duration of fever, most notable in patients started on treatment during the first four days of illness.

We have had an opportunity to treat three patients with tick typhus with paba. One of these had a fulminating illness, the patient dying sixteen hours after admission on the fifth day of the disease. One of the others had a mild case, and treatment initiated on the fourth day resulted in prompt response with cessation of fever on the eighth day. The third was a patient who had serious myocardial damage and failure and peripheral vascular failure, but responded more promptly than we could have expected to a combination of supportive measures and paba. He was fever-free on the fifteenth day, four days earlier than any other patient of this category, though treatment was started on the twelfth day of illness. These patients were first seen too late for optimal treatment, but we were impressed by the fact that they seemed much better within twenty-four hours after starting treatment.

We have also observed the effect of paba in three patients with murine typhus not included in this study because they were not children, but mentioned

\*Hereafter, paba will be used in place of para-aminobenzoic acid and sodium paba for the sodium salt.



because they exhibited a very satisfactory response to adequate therapy. In these patients the temperature fell to normal in less than seventy-two hours after treatment was started, several days before natural termination could be expected, and one very seriously ill adult showed prompt amelioration of symptoms.

The dosage suggested by Tierney<sup>29</sup> may be translated to children by the graph shown in Chart 6. From the studies made concerning sulfadiazine therapy, it has been found that the per pound doses for a 10 lb. infant are approximately 3.3 times as high as that for adults,<sup>31</sup> assuming that the adults treated by Tierney<sup>29</sup> were average in size (150 lbs.). The dosage of 36 Gm. per day were .24 Gm. per pound per day, and infants would be expected, therefore, to need about .8 Gm. per pound per day. It is expected that in older children the dose-weight ratio will follow a curvilinear relationship similar to that illustrated. Our experience as yet does not allow us to offer this curve as a final formulation, but it should serve as a fairly satisfactory means for estimating the maintenance dose needed to bring the infection under control. In practice, it has been our experience as well as that of Tierney<sup>29</sup> that adequate blood levels are achieved slowly, and it is desirable, therefore, to use a large initial dose.

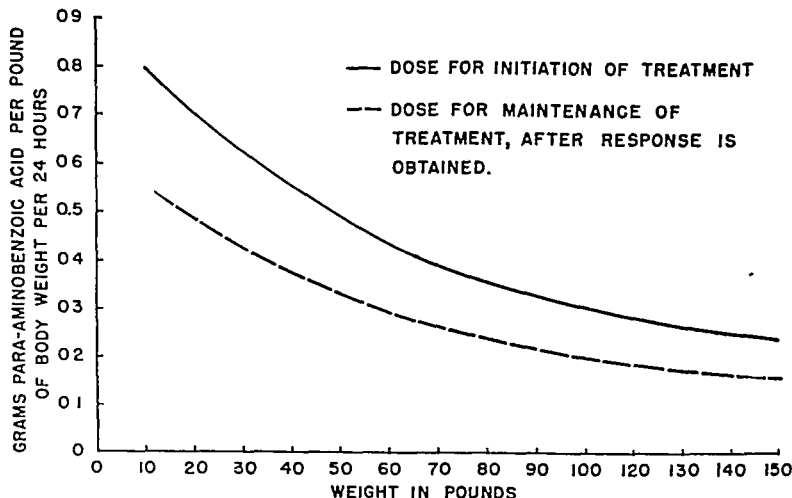


Chart 6.—The dosage of para-aminobenzoic acid in relation to body weight and to the stage of the disease.

The following scheme of therapy, evolved for use in our patients, should yield fairly satisfactory blood levels and prove to be efficacious in the control of rickettsial infections in children.

The total daily dosage, calculated from the initiation level of Chart 6 is divided into twelve doses to be given at two-hour intervals and three times the individual dose is administered as the initial dose. This level of therapy should be maintained until the patient has been fever-free for twenty-four hours. The dosage may then be reduced 25 to 30 per cent or to the level shown for maintenance of treatment after response. The blood levels of the drug should be followed and adjustments should be made to secure levels of 30 to 60 mg. per 100

*c.c. during the late phases of active therapy. Therapy should be continued for some time after a remission of fever is secured to prevent relapses, probably for not less than four to eight days, depending upon the general severity of the infection.*

While no serious toxic manifestations have been noted from paba therapy, mild confusion was noted by Tierney<sup>29</sup> and lowering of the white blood count has been noted by several investigators.<sup>29, 30</sup> Lowering of the polymorphonuclear leucocytes to 2,500 or less per cubic millimeter should serve as a warning to stop therapy or to lower the intake and proceed with caution. It should also be pointed out that paba is excreted in the urine with base and large doses may lead to the development of profound acidosis. The current trend is to use the drug as the sodium salt, sodium paba, instead of as the free acid, and this should obviate this difficulty. Where the plain paba is used, the alkali intake should be supplemented with sodium bicarbonate at the rate of 2.5 to 10 Gm. or more per day to maintain an alkaline urine. Fluid intake should be increased when levels of over 70 are obtained to accelerate the excretion of the drug.

The general supportive treatment of patients with tick typhus is not less important than the specific measures which may be used.

The increased protein needs of these patients has been stressed by Harrell and his associates.<sup>21</sup> They have shown that protein intakes as high as 9 Gm. per kilogram per day may be inadequate to maintain the serum proteins in these patients, but that such a high protein intake simplified the treatment needed to prevent peripheral circulatory failure. We heartily concur in this need for high protein intakes in these patients. These patients should be given a diet high in protein, low in fat, high in free sugars, and having a high calorie value.

This dietary regime unfortunately can only be applied after considerable protein depletion has occurred, and will not serve to combat the peripheral vascular collapse so often found at the time of admission.

This can be countered only by the adequate use of protein-rich fluids (plasma and blood) which will rebuild the blood volume. The magnitude of protein loss in these patients approaches that seen in severe burns and in extreme diarrheal disease and can be combated best by the free administration of large volumes of plasma. The earlier studies of Topping<sup>22</sup> in experimental animals and in patients have shown that the administration of crystalloids intravenously may be associated with a lessening of the patient's chances for recovery. Whether this is associated with an increase in the vascular loss of proteins or with cardiac failure induced by sudden overloading of the heart one cannot surmise from the report. We suspect the first factor to be most important, but we appreciate the real dangers of cardiac failure in these patients.

It is our belief, based on pathologic observations, electrocardiographic findings, and clinical evidence of cardiac failure, that all patients seriously ill with tick typhus should be digitalized. This should be one of the first therapeutic steps in such patients and may be carried out concurrently with the correction of the depleted blood volume.

The larger volumes of plasma and blood which are needed in this correction should be added to the circulation with great care to avoid overloading the heart.

The generalized vascular lesions of the lungs as well as the presence of myocarditis make it imperative to give intravenous infusions slowly.

All other measures useful in combating peripheral vascular collapse, oxygen therapy, large doses of vitamins, especially thiamine and ascorbic acid, and adequate intake of calories, are also important in treating these patients.

In conjunction with the notes on therapy, it should be pointed out that sulfonamide drugs are contraindicated in these patients. It has been shown in experimental animals by Topping<sup>32</sup> and by Steinhaus and Parker<sup>33</sup> that sulfa drugs were inimical to recovery. Martin<sup>34</sup> reported a patient who responded adversely to sulfa drugs and several of our patients were apparently made worse by the administration of sulfa drugs prior to hospitalization.

*Prevention.*—The prevention of tick typhus presents a difficult and complex problem but certain simple rules may be outlined which will aid in lessening the dangers of infection. For most of the country the problem will continue to exist, perhaps in increasing intensity, as it is as yet very difficult if not impossible to eradicate ticks.

For those who must live and work in tick-infested environments, especially in localities where prior cases have been known, there is available a vaccine. This vaccine, developed by Spencer and Parker<sup>35</sup> and improved by Cox,<sup>36</sup> is effective in producing a relative immunity and in bringing about an infection of lessened severity where it fails to protect.<sup>37</sup> Regular, frequent, and systematic search for ticks on the body and their removal should be practiced.

People living and working in such circumstances should make every effort to keep ticks off their bodies by wearing clothes which cover the body, tucking them into shoes and in at the waist. Occasional inspection of the neck will then enable them to keep the ticks off. Ticks, when encountered, should not be handled with fingers, especially should not be crushed. Dogs and other animals should be deticked by insecticides instead of the common practice of picking them off.

#### MURINE TYPHUS FEVER

*General Considerations.*—Murine typhus in man is an acute, self-limited, infectious disease. The etiologic agent is the obligate intracellular parasite, *R. mooseri*. This rickettsia characteristically infects rodents, particularly rats and their ectoparasites.<sup>38</sup> It is transmitted from rat to rat by ectoparasites, principally *Xenopsylla cheopis*,<sup>38</sup> and the rat louse, *Polyplax spinulosis*.<sup>39</sup> The disease is transmitted from the rat to man by the accidental parasitization of man by one of the ectoparasites of the rodent.

The reports of Brill in 1889<sup>40</sup> and 1910<sup>41</sup> first called attention to the fact that there was a mild, noninfectious, typhuslike disease in New York. Subsequent studies by Paullin,<sup>42</sup> Newell and Allen,<sup>43</sup> McNeill,<sup>44</sup> and others,<sup>45, 36</sup> showed that this disease was also present in the South. It was, however, the studies of Maxey<sup>47</sup> in 1926 that really focused attention upon and brought out the real problem presented by this infection. There has been, since that time, as was pointed out by Melency,<sup>48</sup> a rapid extension of the disease to involve new areas and to become more prevalent in the areas where it is endemic.

Maxey's study<sup>47</sup> on purely epidemiologic grounds pointed to rodent population of urban centers as the reservoir for the infection and to some ectoparasite of rodents as the vector. The studies of Dyer and associates<sup>49</sup> incriminated the rat and the rat flea, *X. cheopis*. Subsequent studies have further substantiated this combination as being principally responsible for the spread of this mild form of typhus fever, now generally called murine typhus. The studies of Dove and Shelmire<sup>50</sup> indicate that the rat mite, *Liponyssus bacoti*, which attacks man, is also capable of passing the infection.

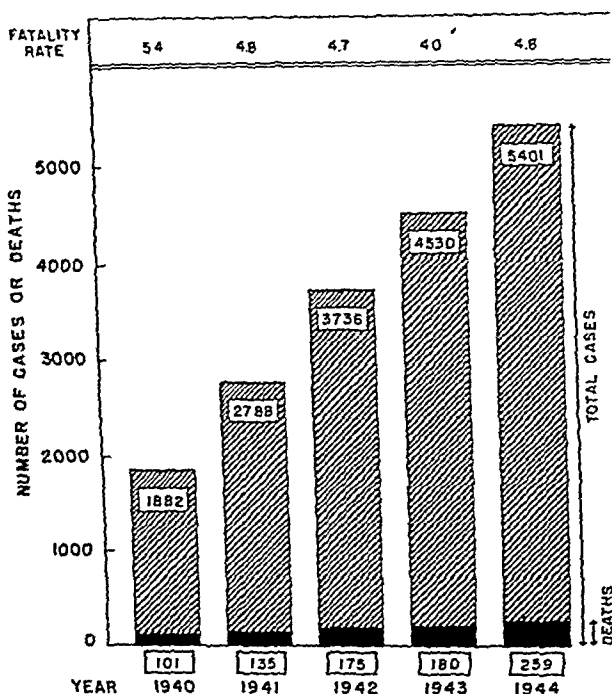


Chart 7.—Cases of and deaths from murine typhus fever in the United States from 1940 through 1944.

The relationship of murine typhus to epidemic typhus is not as yet entirely clear. The development of modern technique for serologic identification of these infections by complement fixation and specific rickettsial agglutination<sup>51</sup> has led to the conception that they are due to closely related organisms but that the organisms are not derivatives of one another. The previously held belief that murine typhus is the result of rodent adaptation of the rickettsiae of epidemic typhus is probably not valid, at least louse transmission of murine typhus does not bring about a reversion to the more severe epidemic typhus.<sup>54</sup>

The problem of typhus fever in this country is wholly that of murine typhus. The problem of murine typhus on the other hand is world-wide and in most parts of the world is complicated by the concomitant presence of epidemic typhus fever. Murine typhus is a danger or potential danger wherever rats are found.

Chart 7 shows the cases of murine typhus reported in the United States in the years 1940 through 1944. The geographic distribution of this infection in the United States is shown in Fig. 6. From this it is apparent that typhus is now chiefly important in the southern states and in the seacoast states except that states north of New York in the east and the sections north of Los Angeles on the west have not yet become areas of serious endemic infection.

In the South the disease has spread from urban centers to the rural sections. It is probable that the disease will increase greatly unless concerted efforts are made to eradicate the rat population. The apathy which is manifested in many areas concerning this problem would make it seem unlikely that relief will occur from this source until the problem becomes worse.

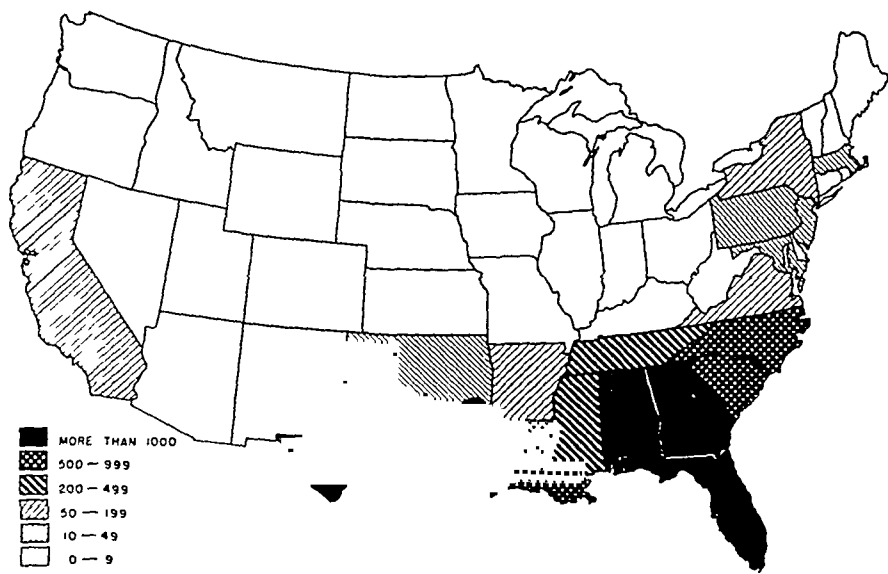


Fig. 6.—Geographic distribution of murine typhus fever in the United States (1940 through 1944).

While there are not adequate studies to show the frequency of typhus fever in children, the study of Baker and associates<sup>52</sup> in Alabama and of Meleney and French<sup>53</sup> in California, indicate that about 10 per cent of the cases are in children. The disease is, as has been shown by Scoville,<sup>54</sup> Eskey,<sup>55</sup> and Davis and Pollard,<sup>56</sup> greatly underreported and underrecognized; and as children have milder infections than adults, it is probable that morbidity in children is considerably in excess of reports. Our own experience bears this out, as we surely missed cases before Scoville's<sup>54</sup> work called to our attention the presence of the disease in infants we were following for mild fever of unknown origin.

There is a distinctive seasonal pattern to the distribution of cases. In earlier studies, Baker and associates<sup>52</sup> were able to show ten times as many cases in September as in February. In recent years there has been less difference, though the greatest incidence is still in the summer and fall months. This is related in part to the degree of parasitism of rats with *X. cheopis*.<sup>57</sup> The seasonal distribu-

TABLE VI. SEASONAL DISTRIBUTION OF REPORTED CASES OF MURINE TYPHUS FEVER IN THE UNITED STATES, 1940 THROUGH 1944

JAN.	FEB.	MAR.	APRIL	MAY	JUNE	JULY	AUG.	SEPT.	OCT.	NOV.	DEC.
679	1,039	615	565	836	1,125	2,109	2,822	2,634	2,286	1,930	1,729

tion of reported cases for 1940 through 1944 is shown in Table VI, composed of figures taken from Public Health Report supplements. From this table it is apparent that cases are prevalent throughout the year but that there are five times as many cases in August, the peak month, as in April, the ebb month.

*Pathology.*—The pathologic disturbances found in murine typhus should provide a background for the understanding of the clinical manifestations. But as at the time of Brill,<sup>41</sup> the pathology of the disease is unknown. Textbooks conveniently refer, without documentation, to a carried-over statement that it is similar to but milder than epidemic typhus. We have been unable to find any protocols of the pathologic histology of murine typhus infections in man. In this city, two cases of typhus have been examined post mortem, both were adults in whom the chief cause of death was cardiac failure and in whom the vascular lesions were minimal. As neither was a completely identified case of typhus, they are not available for detailed study of the pathologic manifestations of the disease. Stuart and Pullen<sup>19</sup> indicate that biopsies of the skin in murine typhus show rickettsias in the vascular endothelium but not in the smooth muscle cells, but they do not cite references.

*Clinical Considerations.*—The onset in murine typhus is abrupt as a rule, with headache, a sense of illness or malaise, abdominal discomfort with nausea and vomiting, chilly sensations, and sore throat being the subjective symptoms noted at the onset. The headache is the most distressing symptom and persists throughout the major part of the illness and was present in most cases. Fever is usually noted immediately after the malaise and headache appear.

Only three of our patients were seen by a physician before admission, one by us as an outpatient and two by other physicians. In each instance the child was treated for a respiratory infection, for sore throat or bronchopneumonia, with sulfonamides.

The children were as a rule apathetic rather than being seriously ill and did not complain much if left alone, which probably accounts for the fact that they were not seen earlier for medical care. Perhaps this may also serve as an index of the degree of severity of the infection.

The fever in our cases varied between 101° and 105° F., and was usually between 102° and 104° F., with a daily variation of 1 to 3° F. The fever tended to swing more widely in the two days before the rapid lysis of one to two days which terminated the fever. Fever persisted for nine days in two instances, eleven days in four, twelve and thirteen days in one each, fourteen days in two, fifteen days in one, and nineteen days in one.

The rash, which is the single specific manifestation of the disease from a clinical viewpoint, appeared from the third to seventh day. In two instances the family had not noted the rash and in one instance the rash was the first symptom noted. The rash is usually thought to appear first on the trunk, usually the

abdomen, and spread peripherally, but our patients did not conform. The rash appeared first on the face or extremities in four instances, first on the trunk in five instances, and was generally distributed when first observed in three instances. The skin lesions were usually pink to red macules 2 to 5 mm. in diameter. These blanch incompletely on pressure but showed purpuric tendencies in only two instances. The rash was usually composed of scattered lesions and was most intense on the abdomen. The rash usually faded, leaving slight brown staining of the skin at the time the temperature began to swing or about seventy-two hours before the fever disappeared.

While these patients were usually quite apathetic throughout the febrile period, coma was not noted at any time, and only two patients could be called stuporous.

Two were brought in with a complaint of stiffness of the neck and slight stiffness was noted on two others at admission. The spinal fluid was examined in seven cases, with a total of eight examinations, on the sixth to eleventh day of the disease, and showed 3, 3, 4, 4, 4, 5, 6, and 8 lymphocytes with 19 to 25 mg. of protein and 55 to 64 mg. of sugar. All evidence of meningeal irritation disappeared with the cessation of fever.

TABLE VII. SERUM PROTEIN DETERMINATIONS IN MURINE TYPHUS

PATIENT	TOTAL SERUM PROTEIN	ALBUMIN	GLOBULIN	DAY OF ILLNESS	COMMENT
T 1	7.1	3.9	3.2	7th	Markedly dehydrated
T 2	6.0	3.3	2.7	7th	Edema of face
T 3	6.0	4.2	1.8	5th	
T 5	6.3	4.1	2.2	5th	
T 6	5.7	3.4	2.3	10th	
T 9	5.9	3.5	2.4	5th	

In two patients, edema of the face was noted. In both instances this was only slight. Serum proteins were determined in six patients (see Table VII). It is apparent from these few observations that while there may be slight to moderate hypoproteinemia in murine typhus, the changes are much less constant and are less marked than in tick typhus. There was not in any of the murine typhus group a shocklike state, though several were mildly dehydrated from poor fluid intake and vomiting. Patient 1 was markedly dehydrated. It is interesting that even in this group with relatively mild arterial lesions the proteins tended to be low and there was a shift of the albumin-globulin ratio toward unit. This suggests that here, as in tick typhus, the principal vascular lesion is one of capillary injury.

There was no evidence of significant renal injury. Patients 1 and 3 showed a slight transient albuminuria. No renal function tests were performed, but in four instances the nonprotein nitrogen was determined, ranging from 27 to 31 mg. per cent.

While five of the twelve complained of sore throat, the examination of the respiratory tract was negative except that ten of the twelve were noted to have some pharyngeal congestion. Chest roentgenograms made in four instances showed only very slight increase in the bronchovascular markings.

There was no evidence in any of our murine typhus cases of cardiac embarrassment. Tachycardia was a usual accompaniment of the fever, but there was no engorgement or tenderness of the liver. Electrocardiograms were made in six instances and showed only slight decrease in the voltage and once minor aberrations in the S-T segment. None showed significant prolongation of the P-R interval.

A number of laboratory studies were carried out on these patients, some of which have already been mentioned and need no further review. The serologic studies which are diagnostic and the hematologic studies warrant review.

There was no particular change in the red blood cells or hemoglobin which could be attributed to the disease. The white blood cells tended, as has been pointed out by Stuart and Pullem,<sup>19</sup> to be low in the first week and then to rise at the end of the second week. Admission counts on the fifth to seventh day were 4,850 to 13,800, with an average of 7,100. Eight of the twelve counts were less than 6,500. Five counts made from the eighth to the tenth day were 5,350 to 9,150, with an average of 6,050, and four counts made on the eleventh to the thirteenth day were 6,500,  $\pm$  1,200.

All patients were examined for their serologic response to the infection as measured by *Proteus* OX<sub>19</sub> agglutination and with two exceptions by complement fixation with the *R. mooseri* antigen. Some were also checked for complement fixation against *R. rickettsii* antigen and the reactions were found to be reasonably specific in this respect. Occasionally much lower titers of heterogeneous rickettsial complement fixation were observed. The complement fixation tests were performed by several laboratories employing antigens of variable sensitivity and specificity. Our series of tests, while not large, indicate that agglutination of *Proteus* OX<sub>19</sub> usually occurs by the tenth day in ten out of twelve patients. A single positive complement fixation test was obtained as early as the tenth day.

In the performance of serologic tests one should remember that the *Proteus* OX agglutinations, while responding more quickly than complement fixation tests, are of no etiologic significance other than to establish the fact that the patient has a rickettsial disease.

The relative sensitiveness of these tests is shown in the following serologic response charts\* (Charts 8 and 9). It is apparent from these charts that there are some cross-reactions between the complement fixation of antigen from *R. mooseri* and from *Rickettsia prowazeki*, and that single determination of low titers might not be specifically significant.

*Epidemiologic Notes.*—Most epidemiologic studies of murine typhus state that multiple household cases are rare, but in our series there were four examples of multiple household infections. Two of our patients were sisters admitted at an interval of more than a year. In one instance there had been three previous cases in the same house. One child was admitted at the same

\*These studies were carried out by the Division of Virus and Rickettsial Disease of the Army, and were made available to us through the courtesy of Major A. D. Scoville.



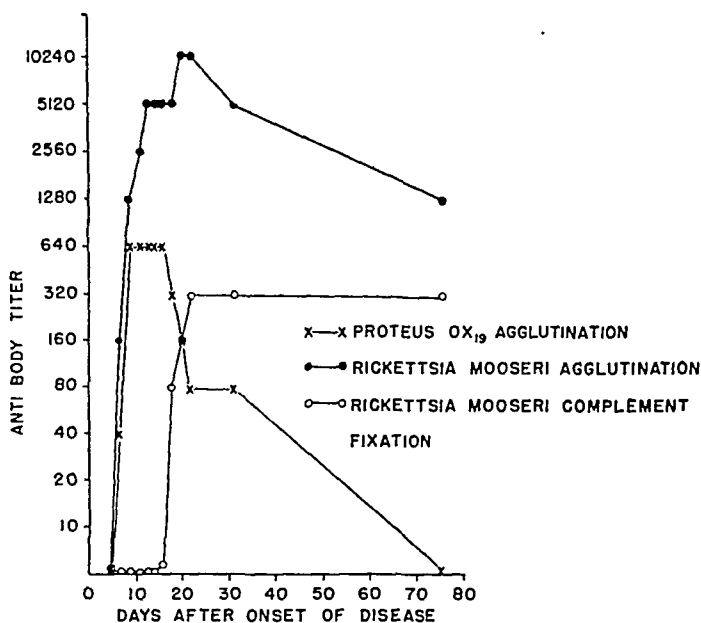


Chart 8.—Antibody response during the course of murine typhus: a comparison of various serologic tests. Case 7.

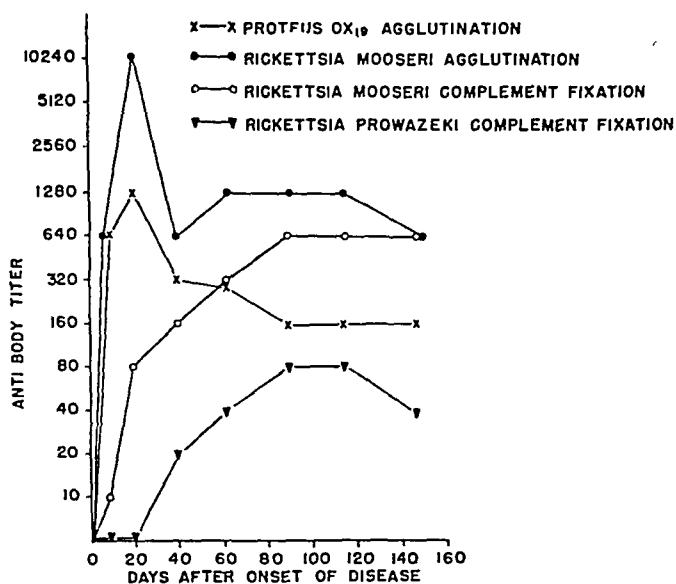


Chart 9.—Antibody response during the course of murine typhus: a comparison of various serologic tests. Case 8.

time as her mother, also ill with typhus, and a brother had had typhus several months earlier. In the other instance, an older sister in the family was recovering from the infection when our patient was admitted. There was no evidence of lousiness in any of our patients. Also, most studies indicate that males are affected more often than females, probably due to the fact that most of the infections considered were the result of infection derived from work association with infected rats. In Nashville, cases originate not only from work association but in some sections from infected rats in residential areas. Scoville<sup>24</sup> has noted that in typhus occurring in such areas the usual preponderance of male cases is reversed and that more women were infected than men. In our group, eleven of the twelve cases were girls. This suggests that the clothing worn by girls makes them more readily attacked by the rat flea, or that their activities in the home are more likely to bring them into contact with the rat fleas. The numbers involved are small but this preponderance is quite startling and significant.

*Differential Diagnosis.*—The diagnosis of murine typhus ultimately rests upon laboratory tests. From the clinical viewpoint, it is essential that a high index of suspicion be maintained; to be recognized it must be kept in mind in all unexplained febrile illness, and even so it will usually be impossible to more than postulate the possibility until the rash appears. The most difficult differentiation with tick typhus was considered in the preceding section.

The disease otherwise is most apt to be confused with exanthum subitum, measles, and drug rashes. In the first of these, marked hyperirritability rather than apathy is the rule, in measles the presence of enanthem and severe coryzeal symptoms should be enough to differentiate the infections. The present custom of treating all patients with infectious processes with sulfonamides makes it most difficult to rule out drug rashes; even the cases of typhus are apt to have been subjected to this treatment. The rash from sulfadiazine would be most likely to be confusing, and that of sulfathiazole rarely if ever. In the most severe cases with hemorrhage into the lesion one might suspect meningococcemia, but here the attendant, relative leucopenia of typhus should be helpful in the differentiation. Typhoid fever with abundant rose spots may at times be confusing but fortunately in this phase the blood culture will almost invariably be positive.

The correct diagnosis could be made eventually by the clinical course of the disease in most instances, but in some sections of the country the severe cases of murine typhus will be confused with mild cases of tick typhus. This differentiation can be made only by the isolation and identification of the specific rickettsia or by running simultaneous serologic tests for antibodies for both rickettsias on the serum, preferably eighteen to twenty-four days after the onset. The fact that the disease is due to rickettsia can probably best be established by the use of Proteus OX<sub>19</sub> agglutinations, a simple test which can be run by any reliable bacteriologic laboratory. The differential diagnosis on the basis of agglutination of strains of Proteus other than OX<sub>19</sub> has fallen, justifiably, into disrepute.

*Treatment of Typhus.*—The fatality rate for murine typhus fever is very low, none in 180 cases reported by Stuart and Pullem.<sup>12</sup> Recovery, in practically

all childhood cases, will ensue with simple expectant treatment which maintains an adequate fluid balance and a reasonable food intake, particularly a high protein intake. This feeding should be by gavage if necessary. Early in the disease the problem of vomiting and associated ketosis may require parenteral administration of glucose, plasma, and saline to reestablish satisfactory metabolic activities and to restore the interstitial fluids. This will be necessary, however, only rarely.

The general outline of therapy for patients with tick typhus is applicable to the more severe cases.

However, even with satisfactory supportive therapy, the disease is a protracted illness with two weeks or more of fever followed by a convalescence period proportional to the age of the patient, which makes the advent of specific therapy highly desirable. The experiences with immune sera in the treatment of epidemic typhus and spotted fever have shown that to be effective these must be given in the first four days of the illness. The practical difficulty in making a diagnosis in this period will almost certainly preclude usefulness of this agent in murine typhus; to say nothing of the costs of such therapy. The observations of Hamilton and associates<sup>24</sup> that paba is effective in inhibiting the lethal effect of *R. mooseri* in the development of chick embryo, and study of Smith<sup>20</sup> showing that murine typhus fever responds to paba when it is administered in the first week of the illness, encourage us to think that the drug will be effective treatment. To be effective, however, early diagnosis and treatment are essential. Our experience with paba therapy in murine typhus in childhood is limited to one patient. This child was treated adequately from the beginning of the fourth day and was fever-free on the sixth day. The technique of using the drug was discussed under the section on tick typhus and needs no repetition here.

*Prevention.*—While laboratory studies indicate that a vaccine would be effective in preventing murine typhus, a more rational approach to the problem would be the systematic eradication of rats.

#### CONCLUSIONS

A review of the rickettsial diseases of childhood reveals that the problem of tick typhus is now common to the whole of the United States and to some areas of Central and South America. The extent of the problem of murine typhus is not now clear, but it probably extends to most of the warmer temperate zones.

Tick typhus is a serious disease with a high mortality even in childhood. A thorough knowledge of the principal pathologic lesions and their relationship to the clinical manifestations of the disease should lead to a more satisfactory handling of these patients. Early recognition of the disease will allow the effective use of paba either alone or in conjunction with serum therapy for the treatment of these patients. To make this early diagnosis the clinician must exercise a high degree of suspicion. It is probable that the increase in travel and utilization of our outdoor recreational facilities, again available to the public, will increase the number of cases of tick typhus.

Murine typhus in the far South is so greatly under-recognized or unreported that we have very little concept of its relation to the practice of medicine. Very likely the disease is masquerading under a wide variety of aliases or exists in a form not now recognized. Though no more than 10 per cent of the cases occur in childhood, one may safely estimate that 5,000 cases occur yearly in children in the United States, chiefly in the southern states. Even though it is a mild disease, its recognition and correct treatment would serve to bring about better medical practice and to emphasize the need for the extermination of rats.

## SUMMARY

1. The clinical manifestations of tick typhus and murine typhus in childhood have been presented and have been correlated, in so far as is possible, with the pathologic and clinical pathologic manifestations of the disease.

2. The general treatment of rickettsial infections in childhood has been presented, together with an outline for the use of para-aminobenzoic acid in these infections.

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# EARLY EVIDENCE OF PSYCHOSES IN CHILDREN

WITH SPECIAL REFERENCE TO SCHIZOPHRENIA

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THE pediatrician is likely to be the first consultant, if not the first physician, to see children with incipient serious illness, mental as well as physical. Since psychoses are known to occur in childhood, and are by definition serious mental disturbances, it seems important for the pediatrician to be familiar with their early manifestations. Some of these early manifestations are the subject of the present report, which is based on studies undertaken to determine what types of childhood behavior signify that a psychosis is present or impending.

In spite of all that has been written and said about psychoses, there is no generally accepted definition of the term. Inevitably in such a situation, concepts as to what constitute psychoses vary among different schools of psychological thought. This is very confusing to the nonpsychiatric worker seeking to orient himself and leaves the pediatrician little choice but to select from some reliable source a definition which will be of practical value to him. For the purpose of the studies herein reported, a psychosis is considered "a severe mental disturbance in which all the usual forms of adaptation to life are involved"<sup>1</sup> and in which "disorganization of the personality is extreme."<sup>2</sup>

A great deal more is known about the psychoses of adults than those of children. They are usually classified as organic, toxic, or functional, depending upon the presence or absence of known causative factors. Individual psychoses in each of the three groups have been fairly well delineated and are often discussed as though they were disease entities. Among the cardinal signs and symptoms helpful in the diagnosis of adult psychosis are the patient's lack of insight that he is ill, the presence of delusions and hallucinations, and apparent disturbance of capacity to sense or express emotions (affect). The implication of chronicity and discouraging prognosis that may accompany the establishment of a diagnosis of psychosis is undoubtedly a by-product of the well-known fact that a large proportion of hospital beds the world over are occupied for years on end by chronically psychotic adult patients.

For children we lack a generally accepted classification not only of psychoses but of psychiatric disorders in general. The criteria mentioned above for adult psychoses do not adequately apply to children for whom we must seek other standards of deviation from mental health. Psychiatric diagnostic standards in childhood must be even more flexible than those used with adults. The reactions of mentally ill children can be properly evaluated only in terms of what is anticipated for most children of similar age and maturity, and no single standard scale of normality covers the entire childhood period.

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Children may react to physical illness or injury with behavior which is sufficiently disturbed to warrant the description "psychotic." The delirium which may accompany fever or some of the disturbances which follow head injury are examples. Such disturbances are, however, not usually listed as psychoses. This may be due to their obviously secondary association with more clearly understood physical illness or to their temporary duration. A classification of such reactions as "symptomatic psychoses" has been recently suggested.<sup>1</sup> While it is generally recognized that a child's usual personality doubtless bears some relation to the temporary mental symptoms that accompany physical illness, we lack precise data proving this relationship. On the basis of information now available, no valid prediction of specific mental symptoms which will accompany the physical illness of a particular child is warranted, nor are we able to discuss this subject at a practical level.

On the other hand, there is considerable information available as to some of the early evidences of functional psychosis in childhood. In contrast to the several clearly recognized functional psychoses of adults, schizophrenia is the only one generally accepted as occurring in children before 13 years of age. This psychosis accordingly forms the main subject of the present discussion.

Schizophrenia was a term introduced by Bleuler in 1911 to describe a mental illness apparently based on a disturbed balance or "splitting" of two important groups of the patient's mental characteristics, those by which he deals with the real world around him and those which are devoted to the imaginary world existing only within his own mind. In mentally healthy individuals these two sets of characteristics are maintained in balance supplementing one another toward efficient mastery of actual life situations. The schizophrenic patient becomes preoccupied with his world of fantasy to a degree incapacitating efficient mastery of these real world situations. Kraepelin in 1896 had used the term *dementia praecox* to describe the illness of many similar patients, emphasizing primarily that it was a mental illness of early life which usually went on to complete incapacity. At present schizophrenia and *dementia praecox* are for practical purposes employed interchangeably in clinical and literary discussions, in spite of their different derivations. "Schizoid" is a related term used to describe personalities and clinical conditions which may precede, lead up to, or are similar to the psychosis schizophrenia.

As applied to children, schizophrenia is best used to denote a psychosis, that is, a severe mental illness. It has been defined for this purpose as "a rare but severe distortion of the personality peculiarly distinguished by a diffuse retraction of interest from the environment. This may be described in terms of the child's diminution of appropriate affective contact with reality, loss of interest in his surroundings, failure to derive emotional satisfaction from the ordinary events of life, or preoccupation with subjective matters to the exclusion of external situations."<sup>2</sup>

#### PLAN OF STUDY

The purpose of the present discussion is to furnish the pediatrician with descriptions, reactions, and behavior which indicate that schizophrenia must be

seriously considered in certain children who come to him for examination, with emphasis on the earliest signs of this psychosis.

In searching for important objective evidence of the presence of psychoses in children, the following three plans of study have been pursued: (1) behavior symptoms capable of description in children presumably psychotic at the time of observation have been investigated and evaluated; (2) past histories of children known to be psychotic have been searched for reports of their earliest maladjustment; and (3) a search has been made for reliable notes written on the spot in diaries or baby books describing step by step the growth and reactions of children who later became psychotic, so that the evolution of a psychosis, in terms used by parents to describe what they have seen, might become available.

Portions of the material herein presented have been previously published but are included as integral parts of the present, more complete report.

#### BEHAVIOR CHARACTERISTICS OF SCHIZOPHRENIC CHILDREN

The initial portion of this study was carried out some years ago and its results published upon completion.<sup>4</sup> Its conclusions have, with minor modifications, since been found valid in a larger number of schizophrenic children over a much wider age range. The project was undertaken to determine just what types of behavior capable of objective description by any intelligent nonbiased observer are characteristic of children whom experienced clinicians have considered to be schizophrenic or schizoid. The investigation concerned 138 maladjusted boys and girls who had been admitted over a period of years for psychiatric study to the Emma Pendleton Bradley Home, a children's psychiatric hospital. All were under 13 years of age and, as resident patients for a period of several months, were free from the immediate effects of family and community pressures and prejudices. Fourteen of these children had been considered potentially schizophrenic by competent clinicians, but their exact criteria for making this diagnosis were variable and often based on intuitive impressions. The study itself was carried out by first tabulating all of the major behavior characteristics of each of these fourteen children as noted in the hospital record. Only reactions capable of description by "persons entirely unfamiliar with each patient's background" were considered. The presence or absence of each tabulated symptom in the total group of 138 children was then checked by several members of the hospital staff who had personally worked with the entire group. The behavior traits whose presence seemed to distinguish the schizophrenic children from the rest were then investigated more carefully.

Eight major behavior characteristics were found to be especially prominent in the fourteen children diagnosed as schizophrenic. These in the order of frequency and apparent importance were as follows:

1. Seclusiveness
2. Irritability when seclusiveness was disturbed
3. Daydreaming
4. Bizarre behavior



5. Diminution of personal interests
6. Regressive nature of personal interests
7. Sensitivity to comment and criticism
8. Physical inactivity

Detailed definitions of these terms appear in the original communication and may be abstracted here:

*Seclusiveness* is considered as a strong tendency to consistently remain aloof from the society of other children for no obvious constructive reason such as physical incapacity, or pursuit of special projects.

*Irritability* is considered to be a reaction of anger when the seclusive activities are interrupted, especially by the personal intervention of other individuals.

*Daydreaming* may be termed apparent preoccupation with thoughts and fantasies definitely beyond what is usually noted in children of similar age and development.

*Bizarre behavior* is made up of actions and activities decidedly incongruous to the surroundings in which they occur. It includes such phenomena as posturizing, repetitive purposeless motions, unintelligible language, and irrelevant expression of emotion.

*Diminution of interests* indicates that there are conspicuously fewer objects and activities toward which the child is attracted than one usually anticipates for most children of similar age and intelligence.

*Regressive personal interests* involve the voluntary selection of and participation in amusements and occupations customarily intriguing children of younger age levels.

*Sensitivity to comment and criticism* implies an excessive emotional response to the personally directed opinions of others such as praise, blame, and so on.

*Physical inactivity* indicates conspicuously less gross motility than is commonly seen in other children of similar age and development.

To illustrate the manner in which these characteristics were noted to be present in one of the children of the schizophrenic group, the following brief clinical history is quoted:<sup>4</sup>

CASE 1.—(Patient 5, Table I.) Dan entered the hospital at the age of 7 because of temper displays, persistent enuresis, and physical attacks upon younger children. His physical condition was excellent.

When permitted, Dan preferred to wander away from any group with which he was playing and enjoyed roaming about in the woods by himself (*seclusiveness*). When attempts were made to dissuade him from these activities, he became sulky, pouty, glared at the supervisor, and muttered under his breath (*irritability*). During school hours he gazed into space and during leisure periods his attention seemed far from his surroundings (*daydreaming*). Dan was frequently observed striking and holding awkward postures. He growled like an animal when alone and showed little obvious emotional reaction to situations and events which should have pleased him (*bizarre behavior*). He seemed to enjoy few activities beyond being alone, daydreaming, and talking to himself (*diminution in number of personal interests*). On the rare occasions when he sought the company of other children he preferred to be with those much younger than himself and often sought attention from them

by using obscene language in a very immature fashion (*regressive nature of personal interests*). When praised he blushed profusely and seemed obviously embarrassed but he cried easily at the slightest scolding (*sensitivity to comment and criticism*). He rarely engaged in the boisterous games common to boys of his age and walked slowly instead of running (*physical inactivity*).

Although this case illustrated the presence of examples of all eight cardinal children's schizophrenic traits, it must not be inferred that a diagnosis depends on so complete a picture in every instance. The group of traits represents rather a symptom-complex of specific observable behavior phenomena which may distinguish schizophrenic and schizoid children from those with other emotional and behavior problems. Table I illustrates the presence or absence of each of the eight traits in the fourteen children clinically diagnosed as schizophrenic in this first group.

TABLE I. BEHAVIOR TRAITS PROMINENT IN FOURTEEN SCHIZOPHRENIC AND SCHIZOID CHILDREN BETWEEN 7 AND 13 YEARS OF AGE

TRAITS	PATIENTS' NAMES AND NUMBERS													
	ALICE 1	BEATRICE 2	CHARLES 3	GWYN 4	DAN 5	ED 6	FRANK 7	HARRY 8	IRA 9	JACK 10	KARL 11	LEN 12	MARY 13	NICK 14
Seclusiveness	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Irritability	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Daydreaming	*	*	*	*	*	*	*	*	*	*	*	*	-	-
Bizarre behavior	*	*	*	*	*	*	*	*	*	*	*	*	-	-
Interests—diminution	*	*	*	*	*	*	*	*	*	*	-	-	-	-
Interests—regressive	-	*	*	*	*	-	*	*	*	-	*	*	-	-
Sensitivity	-	-	-	*	*	*	-	*	-	*	*	*	*	*
Physical inactivity	*	-	-	*	*	*	*	*	*	*	-	-	*	-

It will be noted that seclusiveness and irritability when seclusive activities were interrupted were present in all fourteen children. Because of this, it may at least be assumed that a combination of these two traits is a basic characteristic of this particular symptom-complex. Many of the other individual traits noted may have been secondary to these. In the original communication it was suggested that irritability upon interruption of seclusive activities may well be a measure of the degree to which each child desired to be alone and pursue his solitary way. One does not become irritated, angry, or negativistic when pursuing some object unless that object has meaning and is really desired. This accentuates the fact that each of these schizophrenic children was not merely apathetic and indifferent to others about him but had a strong desire or "drive" *not to share* in their activities.

6 The children in this original group were between 7 and 13 years of age. In searching for early evidence of psychoses it has subsequently seemed important to see whether the same traits were prominent in younger psychotic children. Accordingly, the case records of all patients admitted to the Bradley Home over a period of fifteen years for whom a diagnosis of schizophrenia was suggested were

reviewed. Out of a total of 905 individual children admitted there were thirty-nine under 13 years of age for whom a diagnosis of schizophrenia seemed plausible. To further evaluate the prominence of the eight characteristics previously noted as earliest symptoms, the five youngest patients in the entire group were selected for particular study. These little children ranged from 39 to 48 months of age on admission. The occurrence of the important schizophrenic characteristics in these five children has been tabulated in Table II.

TABLE II. BEHAVIOR TRAITS NOTED IN FIVE YOUNGER SCHIZOPHRENIC CHILDREN BETWEEN 3 AND 4 YEARS OF AGE

TRAITS	PATIENTS' NAMES AND NUMBERS				
	OLIVER 15	PRISCILLA 16	RALPH 17	SAM 18	TOM 19
Seclusiveness	*	*	✓	*	*
Irritability	*	*	*	✓	*
Daydreaming	—	—	—	*	*
Bizarre behavior	*	—	—	✓	*
Interests—diminution	—	—	—	*	*
Interests—regression	*	✓	—	—	—
Sensitivity	—	—	*	—	—
Physical inactivity	*	—	—	*	*

The apparently essential characteristics of seclusiveness and irritability when seclusiveness was interrupted were symptoms common to all five of these younger children, whereas the presence of the other manifestations was possibly less consistent than in the older group. At this earlier age range the particular actions whereby the traits were expressed often varied from what was seen in the more mature and well-developed older children. The following case reports illustrate how some of these manifestations may display themselves in very young schizophrenic children.

CASE 2.—Ralph (patient 17, Table II) was admitted to the hospital nursery school at the age of 3 years and 7 months because of minimal speech development, lack of interest in the activities of others (progressively noticeable for the previous six months), and hyperactive negativistic behavior of gradually increasing intensity. His physical and clinical laboratory status were not abnormal.

Ralph showed no interest in the other children in the nursery school nor in their activities. He spent all of his time in imaginative solitary play (*seclusiveness*). He cried in a frustrated manner whenever his own play was interrupted (*irritability*). If reprimanded he would strike himself. On other occasions he laughed spontaneously and heartily when no external stimulus was evident (*bizarre behavior*). He overreacted to any correction, striking himself as mentioned and occasionally apparently attempting to dominate the attention of adults in a rather playful fashion (*sensitivity to comment and criticism*). There were no extreme evidences of *daydreaming*. His personal interests, though solitary, were fairly wide and adequate for his age and development. His motor activity was that of the usual boy of his age.

Psychometric examination was not feasible with this child. However, his ability to care for all the details of his personal hygiene, his familiarity with the varied and stimulating complicated nursery school schedule, and the particularly playful manner in which he tried to attract the attention of adults suggested potentially adequate intelligence.

Most conspicuous at first glance were his lack of speech, his carefully planned attempts to attract attention, and his apparent fear of new situations. However, over a period of thirteen months' observation, solitary activities and lack of interest in other children and their play seemed dominant and led to a diagnosis of schizophrenic psychosis.

CASE 3.—Sam (patient 18, Table II) was admitted to the hospital at the age of 3 years and 10 months because of loss of speech which he had supposedly acquired prior to 16 months, progressive failure to respond to orders and direction, conspicuous avoidance of people, and unusual interest in printed letters and symbols of all sorts. Repeated physical examinations were negative. The usual hospital laboratory studies were noncontributory.

In the hospital nursery school, Sam showed no interest in the person or activity of other children or adults, paid no attention to suggestions which were given to the group, and was extremely preoccupied with his own solitary play (*seclusiveness*). When this play was interrupted, particularly by any direct suggestion to him, an excessive temper reaction was provoked and he would strike his head against the floor (*irritability*). At times he appeared preoccupied with his own thoughts (though not obviously busy) and in spite of attractive nursery activities about him seemed to be *daydreaming*. He was avidly interested in letters and other symbols of printed form, signs, books, scraps of writing, and children's lettered blocks, and followed out a ritual of bowing his head over such materials (*bizarre behavior*). His only real interest in life seemed to be these printed objects (*diminution of personal interests*). Though limited in amount, these interests could hardly be regarded as *regressive* for a child of his age. No evidence of *sensitivity to comment or criticism* was noted. He was slow in all his motions and rarely gave the impression of being active and alert as is usually seen in the nursery school (*physical inactivity*).

This boy's superior ability in using a pencil, in printing, in recognizing and arranging symbols, and his self-sufficiency in dressing seemed adequate evidence of potential normal intelligence although all attempts at psychometric evaluation failed.

Almost as striking as his exclusively solitary preoccupation with letters and figures was his lack of speech in contrast to well-developed finger dexterity. On the basis of several months' observation, the completely self-centered, inwardly motivated features of Sam's life seemed the basis of these symptoms and led to the diagnosis of a psychosis, presumably schizophrenia.

CASE 4.—Tom (patient 19, Table II) was admitted to the hospital nursery school at the age of 4 years because he had progressively withdrawn from the activities of his home, had failed to develop speech, and was extremely concerned about what he ate, limiting this to a very few foods.

In the hospital this boy disregarded all suggestions made to the group, rarely showed interest in what went on about him, either among children or adults, and preferred to sit alone rocking back and forth and vocalizing in unintelligible sounds (*seclusiveness*). When any attempt to direct him from these activities was made he cried bitterly (*irritability*). Frequent episodes of unprecipitated laughter were noted and his general air of preoccupation suggested *daydreaming*. An infinite number of *bizarre activities* included grimacing with his hand held before him, and vocalizing starting with a low voice which he rapidly raised to a loud shout. He often seemed particularly interested in doors, locks, and gates. His food habits showed a fluctuating interest in special items, what he actually ate being usually chosen on the basis of color or texture rather than because of their taste or quantity. Although he occasionally showed fleeting attention to nursery school activities, he would always return to his own solitary fantasy life (*diminution of interests*). There was no definite evidence of *regressive*

reviewed. Out of a total of 905 individual children admitted there were thirty-nine under 13 years of age for whom a diagnosis of schizophrenia seemed plausible. To further evaluate the prominence of the eight characteristics previously noted as earliest symptoms, the five youngest patients in the entire group were selected for particular study. These little children ranged from 39 to 48 months of age on admission. The occurrence of the important schizophrenic characteristics in these five children has been tabulated in Table II.

TABLE II. BEHAVIOR TRAITS NOTED IN FIVE YOUNGER SCHIZOPHRENIC CHILDREN BETWEEN 3 AND 4 YEARS OF AGE

TRAITS	PATIENTS' NAMES AND NUMBERS				
	OLIVER 15	PRISCILLA 16	RALPH 17	SAM 18	TOM 19
Seclusiveness	*	*	*	*	*
Irritability	*	*	*	*	*
Daydreaming	—	—	—	*	*
Bizarre behavior	*	—	—	*	*
Interests—diminution	—	—	—	*	*
Interests—regression	*	*	—	—	—
Sensitivity	—	—	*	—	—
Physical inactivity	*	—	—	*	*

The apparently essential characteristics of seclusiveness and irritability when seclusiveness was interrupted were symptoms common to all five of these younger children, whereas the presence of the other manifestations was possibly less consistent than in the older group. At this earlier age range the particular actions whereby the traits were expressed often varied from what was seen in the more mature and well-developed older children. The following case reports illustrate how some of these manifestations may display themselves in very young schizophrenic children.

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Psychometric examination was not feasible with this child. However, his ability to care for all the details of his personal hygiene, his familiarity with the varied and stimulating complicated nursery school schedule, and the particularly playful manner in which he tried to attract the attention of adults suggested potentially adequate intelligence.

Most conspicuous at first glance were his lack of speech, his carefully planned attempts to attract attention, and his apparent fear of new situations. However, over a period of thirteen months' observation, solitary activities and lack of interest in other children and their play seemed dominant and led to a diagnosis of schizophrenic psychosis.

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This boy's superior ability in using a pencil, in printing, in recognizing and arranging symbols, and his self-sufficiency in dressing seemed adequate evidence of potential normal intelligence although all attempts at psychometric evaluation failed.

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*interests* aside from these bizarre activities of undeterminate maturation level. He showed no evidence of *sensitivity to comment and criticism*. He stood about or sat so much during his solitary activities that he gave the impression of a much less *physically active* boy than others of his age group.

Formal psychometric examination could not be carried out with any degree of reliability. However, Tom's keen recognition of foods of certain texture or color, the ingenious methods he used to secure them at the table, and his self-sufficiency in caring for his dressing and similar needs all suggested potentially normal intelligence.

His bizarre activities, particularly those relating to his feeding habits, were his most obvious symptoms. Complete lack of speech was almost as conspicuous. Over an 11-month period of observation, the extremely self-absorbed, apparently internally motivated nature of all his behavior was sufficiently impressive to lead to a diagnosis of schizophrenic psychosis.

In what has been said so far an attempt has been made to demonstrate that the basic elements of the behavior of schizophrenic children can be observed and can be recorded in nontechnical language by observers who need not be experts provided they are relatively free of bias and prejudice. These behavior characteristics seem to apply to psychotic children down to very tender ages. Whether or not they are evidences of psychosis in its earliest developmental stages, they are certainly evidences of psychosis in the very early life stages of individual psychotic patients.

#### EARLIER EVIDENCES OF MALADJUSTMENT

In an attempt to search back further into the lives of children who were later thought to be psychotic, the early histories of all thirty-nine schizophrenic children admitted to the Bradley Home over a fifteen-year period were carefully reviewed. Thirty-two of the histories contained specific descriptions of behavior and development in infancy and earliest childhood. In the remainder this information was lacking so that these seven histories were discarded for the purposes of this part of the study. Evaluating the information obtained from the thirty-two reliable early histories, it must be noted that the material was taken from the usual hospital records and not obtained as any part of a research project. Since there were no siblings in this series, informants were thirty-two different sets of parents and relatives. Moreover, the histories were obtained by a number of different staff physicians over a period of several years. Any points of agreement in data obtained from the histories of this many children under the variables which these conditions impose may obviously be of some clinical significance.

*Age of Earliest Noted Maladjustment.*—In searching for specific statements to indicate the earliest age at which evidences of maladjustment had come to parents' attention it was striking that in twenty-nine out of the thirty-two children definite evidence of this sort had been present before 2 years of age. Thirteen of these children were recalled as having presented definite problems at ages which were specifically recalled as "before one year," "at 16 months," "before

2 years," etc. In the remaining nine cases "infancy" only was specified. From the nature of the complaints in the entire group and the way in which the information was obtained, two years seems a reasonably conservative upper limit of what was implied when "infancy" was mentioned and not qualified by more specific dates.

*Nature of Earliest Noted Maladjustments.*—The precise behavior symptoms noted in these hospital histories as occurring during the first two years of life were quite diverse. For some, isolated symptoms, and for some a variety were reported. The positive statement most frequently made indicated that a child had shown a lack of interest in his surroundings, particularly in other persons, during this early age period. This was reported for twelve children.

Next to this lack of interest the most common observation was retardation or failure of speech development, occurring in eight children. In six others in whom speech had apparently been developing normally, it disappeared during the infancy period. Thus a total of fourteen children gave some evidence of disturbed speech development.

Nine children had presented feeding problems of various sorts, some extremely severe but none particularly characteristic of the group as a whole.

Conspicuous hypermotility and hyperactivity were distinctly recalled by the parents of six children.

These symptoms of diminished interest, retardation, or interruption of speech development, feeding problems, and increase of motor activity were by no means all the early signs of maladjustment reported. None of the great variety of others, however, occurred in sufficient frequency to warrant special mention.

#### LONG-TERM STUDIES OF INDIVIDUAL CHILDREN

The entire psychiatric literature contains but two detailed long-term studies of children who were thought to be schizophrenic in early childhood and for whom details of early development in the form of notes were kept in diaries by their parents.<sup>5, 6</sup> It has been the writer's privilege to have access to one of these documents which has previously been edited and published.<sup>6</sup> A brief résumé of the outstanding features of this girl's early development may be of interest.

CASE 5.—Gwen (patient 4, Table I) was an only child. A personal and professional acquaintance by the author with her parents and numerous relatives has revealed no serious abnormalities of parental maladjustment or familial defect. The father was of superior education and enjoyed enough leisure time during his daughter's early childhood to keep a detailed diary starting at a considerable period before any abnormality or serious problem was even suspected.

After an apparently uneventful pregnancy, birth, and early development Gwen, at 8 months of age, began to show a violent dislike to having any other child in the play-pen with her. At this same age it is recorded that she "smiled less than other children." At 9 months she was noted to scream when neighborhood children merely looked into her carriage. At one year of age she would shut her eyes and turn away from any strangers. At 18 months she seemed contented only when playing by herself.

Gwen's speech development was somewhat retarded. She was 17 months old before she was heard to speak her first word. At 2 years she used single words only. When she was 3 years old, she was said to be talking in a very "parrot-like" fashion.



Details of Gwen's subsequent development have been reported elsewhere, but following her admission to the Bradley Home her outstanding characteristics were described as follows:

She kept away from other children whenever possible and when physically close to them did not converse. She was frequently seen standing behind the door of her room muttering and often lay motionless on her bed with her eyes half closed and a rapturous expression on her face (*seclusiveness*). If these solitary activities were interrupted, she would scowl and vehemently express her displeasure (*irritability*). She paid little attention to her work in school, often sitting for long periods with eyes closed or gazing into space while otherwise unoccupied (*daydreaming*). There was a great deal of *bizarre behavior*, examples of which were urinating out of the window or into her shoes, defecating in her clothes locker, frequently grimacing, often refusing to respond to questions, and at every opportunity assuming unusual postures such as lying on the floor with legs uplifted and underclothes exposed regardless of who might be observing her. Her *interests were diminished*, and although she rarely paid attention to what was going on about her, conversation revealed that she missed few details. Her bizarre exploratory activities, considerable masturbation, and finger play suggested that her *interests were regressive* in nature. If she were corrected or scolded, she sometimes cried and usually reminded members of the staff that no one liked her. In addition, she expressed ideas that adults whom she could see but not hear were being critical of her and in many other ways appeared *sensitive to comment and criticism*. She spent so much time alone and so often refused to participate in other children's games that the impression she gave was one of *physical inactivity*.

There appeared unexplained mood swings and variation in interest and activity from time to time, but over a long period of hospitalization no fundamental change or improvement was noted. Gwen's preoccupation with her own fantasies and her disdain for any of the activities of others remained quite constant and, when supplemented by the other details mentioned, led to a diagnosis of schizophrenic psychosis at the age of 8 years.

This brief résumé of a voluminous long-term study is used to illustrate the evolution of problems present in infancy to the symptom-complex of behavior traits mentioned above. There is an obvious need for many more such studies if we are to understand adequately the early evidences and development of psychoses in children.

#### COMMENT

These attempts to describe behavior which may be characteristic of schizophrenic children were originally motivated by a desire to secure from the study of patients themselves information which would remove from the diagnosis of childhood schizophrenia the inconsistencies with which conflicting psychological theories and the dependence on clinical intuition had previously surrounded it. While the traits enumerated are clearly at a descriptive level only, the importance of observation and description as aids in diagnosis needs no justification. In the early differential diagnosis of a child's behavior disorder, the first impressions received by the physician are derived from what parents and others tell him of the patient's behavior. They are usually next supplemented by what the physician himself may observe. If both the history and symptoms suggest extreme seclusive tendencies in combination with several of the other eight traits that have been described, and are supported by a story of maladjustment going back into earliest childhood years, the possibility of schizophrenia must be considered and more complete psychiatric study advised.

It is beyond the scope of this communication to discuss in any detail the possible causes of schizophrenic reactions in children. More comprehensive re-

views<sup>7, 7</sup> indicate that no appreciable proportion of reported cases can be traced to any specific abnormalities of heredity, the prenatal state, birth and medical history, life experiences, intellectual capacity, or recognizable physical characteristics. That the specific reaction can appear so early and is usually preceded by definite though less specific evidences of inability to meet the demands of life even in infancy suggests that a constitutional predisposition is the basic handicap. This naively expressed concept is not as impractical as it may sound, since it allows us to recognize that physical or emotional trauma only precipitates or intensifies the pathologic reactions to which the patient is intrinsically predisposed. In other words, the many suggested causes of schizophrenia (ranging from parental overprotection and unstable or dominant mothers to early injury of the nervous system and endocrine imbalance) may intensify symptoms to the point of attracting clinical attention but should not necessarily be considered the particular objects of treatment in the case of every schizophrenic child.

Obviously not all seclusive children are potentially schizophrenic nor is all infantile maladjustment the precursor to psychosis. The intensity and persistence of reactions such as those described are quite as important for diagnostic purposes as their quality. Mild or brief episodes of schizoid behavior may be noted at times of stress or illness in some children whose previous and subsequent adjustment is entirely adequate. A definite and serious diagnosis is justified only upon repeated or prolonged observation of significant reactions either in a variety of situations or in a setting where the child is temporarily free from external complicating factors.

Since schizophrenia in children appears to be a way of life rather than a disease, its existence is not incompatible with that of other handicaps such as mental deficiency, epilepsy, or cerebral palsy, to mention only a few coexisting conditions that have come under the writer's observation.<sup>3</sup>

Treatment and prognosis are further complex subjects outside the province of this presentation. Therapy is basically a problem of eliminating or reducing factors which intensify the child's fundamental maladjustment.<sup>3, 8, 9</sup> It is essentially a psychiatric problem, since modifications of parental attitudes, alleviation of secondary symptoms, and special educational programs are involved. Ultimate prognosis depends both upon the degree to which remediable factors can be successfully brought under control and the degree to which constitutional predisposition is present.<sup>3, 10</sup> The latter is generally assumed to be severe if schizophrenia is apparent at an early age. While no invariable course and outcome can be predicted, a well-substantiated diagnosis of schizophrenia in childhood carries with it a serious prognosis.

#### SUMMARY

In a study of schizophrenic children in the controlled environment of a children's psychiatric hospital, eight behavior characteristics were noted to distinguish these patients from other seriously maladjusted children. These traits were diagnostically significant as early as the fourth year. A review of

the early histories of schizophrenic children revealed evidence of maladjustment before 2 years of age in most instances. The significance of these early evidences of psychosis in young children is considered.

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## STREPTOMYCIN: A REVIEW

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IT HAS been said that, whereas the discovery of penicillin was, in a sense, accidental, streptomycin came to light in the course of a premeditated and carefully planned search for just such a drug. Biologists, of course, had long noted the phenomenon of antibiosis, and an almost unbroken succession of laboratory workers and clinicians, stemming from Pasteur, have sought to exploit its implicit therapeutic possibilities.

Waksman of Rutgers University, long noted as a soil microbiologist, had undertaken, in the late 1930's, the onerous task of screening his microorganisms, new isolates as well as stock cultures, in a series of tests designed to uncover any cultures whose metabolic products might, after extraction and purification, meet the exacting requirements of clinicians. Several powerful new antibiotic substances came to light, but it was not until 1943 that his group found one that gave promise of meeting these requirements. An Actinomycete, apparently *Streptomyces griseus*, an inhabitant of garden soils, river muds, peat, and compost heaps, was found to produce a substance exhibiting powerful bacteriostatic activity, especially against many of the gram-negative pathogens not sensitive to penicillin. Among the more susceptible of these in agar-dilution tests were *Brucella abortus*, *Eberthella typhosa*, *Escherichia coli*, *Hemophilus influenzae* and *Hemophilus pertussis*, *Klebsiella pneumoniae*, *Pasteurella tularensis*, *Proteus vulgaris*, *Pseudomonas aeruginosa* (relatively resistant), and *Salmonella schottmuelleri*. In addition, a pathogenic human strain of *Mycobacterium tuberculosis* was found to be inhibited. Later in vitro tests added a number of additional pathogenic species, including *Bacillus anthracis*, *Brucella melitensis* and *Brucella suis*, *Corynebacterium diphtheriae*, *Neisseria gonorrhoeae* and *Neisseria intracellularis* (meningitidis), *Pasteurella pestis*, *Proteus ammoniae*, *Salmonella enteritidis*, *Shigella paradysenteriae*, *Streptococcus faecalis* (relatively resistant), and *Actinomyces bovis*. Penicillin-sensitive gram-positive aerobes were not notably affected, and anaerobes, fungi, and viruses not at all. When extracted and partially purified, the active substance was found to be encouragingly stable and relatively nontoxic for laboratory animals.

The discovery was announced in January, 1944, together with information on culture media and a method for extraction and concentration of streptomycin from culture filtrates. Before the end of 1944, transplants of the active cultures (not all isolates proved to be equally productive) were distributed to numerous industrial laboratories, where the formidable resources of equipment, man power, and "know-how," only recently marshalled for penicillin, were concentrated on the more difficult task of developing workable production methods. For it was realized by the Rutgers group that without the help of industry it

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portion is a diguanido inositol and the streptobiosamine is made up of an unnatural (levo) optical isomer of N-methyl glucosamine and a hitherto unknown branched-chain hexose (streptose or streptonose) bearing two aldehyde groups. The streptidine and streptobiosamine are joined in the parent streptomycin by a glycoside linkage of the streptonose portion of streptobiosamine to one of the oxygen atoms of streptidine. One suggested chemical assay method is based on the formation and colorimetric determination of maltol (a previously known compound) from the streptonose portion of the intact molecule upon treatment with alkali. On the basis of present knowledge, the molecule can be varied only at the aldehyde group in the middle fragment. Oxidation to the organic acid destroys its activity. Reduction to the aldehyde increases the alkali stability of the compound and does not materially change its in vitro activity. Suffice it to say that a structure so complex and unfamiliar offers even less hope than does that of penicillin for artificial synthesis.

Consequently, we are dependent for streptomycin on natural biosynthesis. Being an aerobic organism, *S. griseus* must be cultivated aseptically on the surface of suitable liquid media or throughout the medium in large culture tanks through which large volumes of sterile air are bubbled under controlled conditions. The organism produces relatively minute amounts of streptomycin—at present not much more than 0.0001 Gm. per milliliter of the culture liquid. This precious fraction must be extracted and purified by an exacting procedure involving filtration, adsorption, elution, concentration, and desiccation; inevitably, much is lost in the process. The final product is an almost colorless powder, sterile, free of pyrogenic substances, free or almost free of histamine-like activity, safe for injection, and remarkably stable. Since the free base is unstable, the streptomycin is present in the form of a salt, usually the hydrochloride or the sulfate. The potency of these preparations is at least 300  $\mu$ g. of pure streptomycin base (or "S units") per milligram of powder. Since a milligram of either of these salts, when pure, contains approximately 800  $\mu$ g. of streptomycin base, the powders now available contain at least 40 per cent of active streptomycin base. The powder is readily soluble in water; when reconstituted with sterile, pyrogen-free water in a concentration of 100 or 200 mg. of streptomycin base per milliliter, it forms a clear solution of pH 5.0 to 7.0. Solutions for injection may be prepared either with water or with physiological saline solution.

Throughout the manufacturing process, progressive concentration of the active material is followed closely by means of potency assays. Rapid and precise chemical methods are being sought, but at present two biologic methods are in common use, an agar-diffusion method employing a strain of *Staph. aureus* or more commonly *Bacillus subtilis*, and a turbidimetric method employing a nonencapsulated strain of *K. pneumoniae*. Assays of pharmacologic and clinical samples for following streptomycin concentration in body fluids have been performed by Fleming's slide-cell method with *Bacterium megatherium* or by a serial-dilution endpoint method with broth cultures of *K. pneumoniae* or *Bacillus circulans*. In all methods, the samples are compared with corresponding dilutions of a streptomycin preparation of known potency, based on the working

might take years to produce sufficient material for the crucial clinical tests on which the future of this apparently safe and powerful antibacterial substance would necessarily depend. In less than a year streptomycin was in limited production, further animal studies were completed, and clinical trials were under way. Shortly thereafter, eleven manufacturers contributed nearly one million dollars to the National Research Council for a comprehensive program of clinical trials under the supervision of Dr. Chester S. Keefer. It soon became apparent that Waksman's hopes were destined to be at least partially sustained. By 1946, the limitations of this new drug were fairly well defined, specifications were drawn up by military and civilian control agencies, and its probable therapeutic value was forecast.

Production, which had been about 3 kg. during September, 1945, increased to almost 40 kg. for May, 1946, and reached slightly over 200 kg. for December, 1946. Certification of individual lots for civilian use is not legally required at present, but all members of the industry have voluntarily agreed to submit samples of each lot to the Food and Drug Administration before release.\* On Sept. 1, 1946, the Civilian Production Administration designated 1,652 hospitals to serve as regional depots for the controlled commercial distribution of streptomycin for civilian treatment. By November, the supply had increased sufficiently to justify relaxation of controls; since that date, hospitals and sanatoriums have been permitted to order the drug direct from suppliers of their choice. The Civilian Production Administration still allocates domestic and export release quotas from each manufacturer or supplier, and the Office of International Trade of the United States Department of Commerce controls distribution of export quotas among various exporters. But since Dec. 1, 1946, domestic sale, within allocation, has not been restricted and is now handled through normal trade channels. It is hoped that additional manufacturing facilities now under construction will increase the supply of streptomycin sufficiently within six months to justify lifting of the present allocation system. During recent months, the cost of the drug has been halved twice with the result that, weight for weight of equivalent pure material, it is now as cheap as penicillin.

Streptomycin is an organic base, soluble in water and insoluble in most organic solvents. It may be considered as related to sugars (in contrast to penicillin which is more related to amino acids). From partially purified hydrochloride or sulfate salts it has been possible to prepare three crystalline salts, the helianthate, and the double salts reineckate sulfate and trihydrochloride-calcium chloride. A derivative, dihydrostreptomycin, has also been prepared by catalytic hydrogenation of streptomycin hydrochloride or the trihydrochloride-calcium chloride double salt. The calculated formula for streptomycin is  $C_{27}H_{50}N_7O_{12}$ . As a result of experimental work by numerous organic chemists, the general structure of the molecule is now well defined. The molecule has been split into two components, streptidine and streptobiosamine. The streptidine

\*On March 10, 1947, President Truman signed the streptomycin amendment (H. R. 2045) to the Federal Food, Drug, and Cosmetic Act. This amendment places streptomycin on the same basis as penicillin, including the requirement that samples of each manufactured lot be submitted to the Food and Drug Administration and certified by the administration before the lot is released for distribution.

be injected into the pleural or peritoneal cavity. Dry mixtures with lactose (250 mg. per gram) or aqueous solutions (50 to 100 mg. per milliliter) may be applied topically.

While it is true that even relatively pure streptomycin sometimes produces unpleasant side reactions, particularly when massive doses are administered over long periods of time, yet the drug is remarkably free of toxicity and, excepting penicillin, is safer than any chemotherapeutic agent yet found. Certain patients exhibit familiar types of drug sensitivity, including pain and tenderness at local site of injection, headache, fever, skin eruptions, tachycardia and fall in blood pressure, paresthesias about the face, and flushing of the skin. Those under prolonged courses of treatment for stubborn inaccessible infection such as tuberculosis eventually exhibit eighth-nerve disturbances: vertigo and tinnitus disappear when treatment is suspended; deafness is apparently often irreversible, but is more or less readily compensated. In short, streptomycin is hardly indicated where cheaper or less irritating agents will serve equally well, but may be used without hesitation where the prognosis is poor or where other means of treatment are inadequate, and especially in cases where laboratory tests on the isolated culture show the infecting organism to be streptomycin sensitive.

Streptomycin has been found to evoke a multifold increase in resistance to its action on the part of many organisms, not only *in vitro* but unfortunately also *in vivo*. This increase in resistance may be brought about in part by the action of serum and of other factors within the body, in part by selective action of the drug, resulting in unhampered multiplication of relatively resistant individuals and concomitant elimination or possibly mutation-like alteration of the more sensitive individuals. Hence, as with the sulfonamides and penicillin, it is safest and most effective in the treatment of infections which will respond quickly to massive, briefly sustained medication.

Where streptomycin therapy has failed, at least one of five causes has been assigned: (1) the organism was not sensitive to streptomycin; (2) dosage was inadequate; (3) the organism became resistant during treatment; (4) the predominant species of infecting organism changed during treatment; (5) infection became localized in an area inaccessible to streptomycin. It is hardly necessary to point out that bacteriologic studies could have prevented or at least directed prompt attention to each of the first four causes of failure.

Although clinical experience is now accumulating rapidly, it is still too early for a full evaluation of streptomycin, and this is especially true of relatively inaccessible chronic infections such as leprosy and tuberculosis. A study of ten patients at the National Leprosarium just completing a seven-month course of treatment, five of them with sulfones and five with sulfones plus streptomycin, indicates that while streptomycin produces encouraging results, its cumulative toxicity when administered in large and continuous dosage (1 or 2 Gm. a day) is such that, alone, it will probably not become the drug of choice in leprosy. Although streptomycin is the most dramatically efficacious chemotherapeutic agent yet found for the treatment of tuberculosis, permanent benefit in long-standing infections, and in meningeal or miliary forms of the disease



standard distributed by the Food and Drug Administration from pooled lots of streptomycin sulfate contributed by most of the manufacturers.

Although the *in vitro* sensitivity of an organism cannot, unfortunately, be taken as an infallible guide to its sensitivity within the body, it is generally agreed that the infecting organisms should be isolated from candidates for streptomycin therapy and that the streptomycin sensitivity of the organisms should be determined both before and throughout the course of treatment. The value of such *in vitro* tests is now known to be affected, in part at least, by their character, for it has been shown that the *in vitro* sensitivity of an organism to streptomycin is influenced by many factors, including age of culture, concentration of organisms, growth phase of the culture, and constituents of the medium used.

When therapeutic blood levels are sought, streptomycin can be injected by the common parenteral routes. Since adequate blood levels can be established in less than two hours following intramuscular administration, there is little to recommend the more speedy intravenous route (except in fulminating cases of bacteremia) or the more painful subcutaneous route. Blood concentration has been found to be generally proportional to the size of the dose, a sustained level of 10  $\mu\text{g.}$  of streptomycin base per milliliter of blood being attained with 0.6 Gm. a day, and a daily dose of 1.5 to 2.0 Gm. being found necessary to raise the blood level above 16  $\mu\text{g.}$  per milliliter. Serum levels of 32  $\mu\text{g.}$  per milliliter have been maintained with daily parenteral administration of 3 Gm. Absorption is more rapid from saline than from peanut oil and beeswax. Following intramuscular injection, streptomycin is readily distributed throughout most of the body fluids and has been found in fetal cord blood and amniotic fluid. Much of it concentrates in the kidneys, whence 50 to 75 per cent of the total amount administered is excreted with the urine within twenty-four hours. It is thus possible to maintain drug levels in excess of 100  $\mu\text{g.}$  of streptomycin base per milliliter of urine by parenteral dosage at a rate considerably less than 1 Gm. a day. A small portion is also excreted in the bile. Streptomycin does not readily diffuse into the cerebrospinal fluid of normal persons; but when administered parenterally to patients with meningitis, amounts sufficient to check growth of susceptible bacteria may reach the cerebrospinal fluid after repeated injections. Larger intracisternal levels can be obtained by supplemental intrathecal injection of 25 to 50 mg. a day. Oral administration is contraindicated where systemic drug levels are required, because no appreciable amounts of streptomycin pass through the gastrointestinal wall; likewise, parenteral administration is valueless in the treatment of gastrointestinal infections. However, since the drug retains its activity in the gut, oral administration of 2 to 4 or 5 Gm. per day is strikingly effective in reducing or obliterating the fecal flora and thus, apart from its curative effect in some cases of bacillary dysentery, offers a useful sanitation procedure prior to operation on the colon. Similarly, although streptomycin is not absorbed to any appreciable extent through normal lungs, inhalation of nebulized streptomycin provides a valuable supplement to penicillin in preparation for pleural surgery as well as in the treatment of some cases of chronic pulmonary suppuration. Solutions containing  $\frac{1}{10}$  to 1 Gm. may

## OSSEOUS CONGENITAL SYPHILIS: EFFECTS OF PENICILLIN ON RATE OF HEALING

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OSSEOUS congenital syphilis is a dynamic process which waxes and wanes as the infant grows older, and late complete healing may be expected even when early lesions are severe. Evaluation of antisyphilitic treatment for this self-limited process is impossible unless the natural history of untreated osseous syphilis is kept clearly in mind. The course of untreated osseous syphilis may be altered by several factors, of which the most important would seem to be the age of the fetus at time of infection and the adequacy of treatment of the mother. Although fetal infection may take place as early as the fifth month, it frequently does not occur until just before parturition, even when the mother has been infected much earlier.<sup>1</sup> Therefore, the duration of the fetal infection before appearance of osseous lesions<sup>1</sup> cannot be determined accurately. It has been stated<sup>2, 3, 4</sup> that evidences of active syphilis seldom develop in newborn infants of syphilitic women who have received moderate or large amounts of antepartum treatment; and osseous lesions, if present, disappear within a few weeks. When we assume that adequate maternal therapy is responsible for rapid healing of fetal osseous lesions, we must consider two factors: First, in infants subsequently proved to be syphilitic, osseous lesions are commonly absent during the first few weeks of extrauterine life.<sup>5, 6, 7</sup> Second, in the newborn infant, many minor osseous abnormalities roentgenographically compatible with syphilis, but actually secondary to other disturbances, may be of a transitory nature.<sup>2, 5, 8, 9, 10</sup> Caffey<sup>11</sup> has indicated the many pitfalls that may be encountered in an unequivocal roentgenologic diagnosis of osseous congenital syphilis.

McLean's<sup>12</sup> classification was adopted for this study. For purposes of statistical analysis an arbitrary weight of severity was assigned to each type. The authors assume full responsibility for these arbitrary criteria which, although they may be found wanting with further experience, do have some merit for current purposes.

*Osteochondritis.*—(Fig. 1.) *Type I* consists of a single thickened line of increased density at the end of the metaphysis. It is nonspecific and may be encountered in a wide variety of conditions which produce disturbances in growth of cancellous bone. Some of these are malnutrition, bacteremia, miliary tuberculosis, hemolytic disease of the newborn, acute leucemia in the infant, and

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appears doubtful. Its greatest usefulness will probably be as an adjuvant in the treatment of those early forms of tuberculosis likely to be permanently benefited by one to two months of streptomycin treatment; that is, early, acute, progressive, exudative forms of pulmonary tuberculosis with or without thin-walled cavities, and ulcerating lesions of the larynx, hypopharynx, tracheobronchial tree, and sinus tracts. The daily dose has usually been between 1.5 and 3 Gm. While "the place of streptomycin in tuberculosis therapy has not been fully determined," it appears, in the words of the Mayo clinicians, "to have a very great usefulness which is much more likely to supplement than to supplant the proved effective standard methods of treatment."

Streptomycin therapy appears to be the best treatment available for tularemia ( $\frac{1}{4}$  to 1 Gm. daily for five to seven days) and for mild or moderately severe meningitis due to *H. influenzae* and to several of the other commonly encountered gram-negative organisms. For influenzal meningitis, the suggested daily dose is  $\frac{1}{2}$  to 1 Gm. intramuscularly, plus 25 to 50 mg. intrathecally, for five to seven days. Streptomycin has been found effective in children against severe influenzal meningitis of types other than b when supplemented with sulfadiazine, and against severe type b influenzal meningitis when supplemented with rabbit antiserum as well as sulfadiazine. Respiratory and other infections with *H. influenzae* have also responded satisfactorily.

Streptomycin is indicated for gram-negative bacteremias (2 to 4 Gm. daily for five to ten days) and for many heretofore resistant infections of the urinary tract (1 to 3 Gm. daily for five to ten days), especially those due to proved streptomycin-sensitive strains of *H. influenzae*, *K. pneumoniae*, *P. vulgaris*, *P. ammoniae*, *Ps. aeruginosa*, *Esch. coli*, *Aerobacter aerogenes*, and *N. gonorrhoeae*. To succeed in such urinary-tract infections, urination should be unimpaired, the urine should be alkalinized, and marked benefit should result within three days. Many cases of gram-negative peritonitis, Friedländer's pneumonia, liver abscess, cholangitis, heart-valve invasion, chronic pulmonary infection, and empyema due to organisms of demonstrated streptomycin sensitivity have responded well to streptomycin therapy (usually 2 to 4 Gm. daily for five to ten days). Army surgeons have obtained excellent results with streptomycin applied directly to the external ear, to pleural cavities, and to brain infections. The place of streptomycin in the treatment of various enteric infections is still in doubt, although many cases of bacillary dysentery have improved under oral streptomycin therapy, usually supplemental to parenteral administration.

Its value in typhoid fever, salmonella infections, brucellosis, and cholera is questionable, but its attempted use may be justifiable in some severe cases (3 to 5 Gm. daily for ten to fourteen days). Streptomycin is ineffective in malaria and in infections due to Rickettsiae, viruses, Clostridia, and fungi.

These remarks have been necessarily discursive and superficial. If they have helped to outline the background and nature of this very new antibiotic substance and to indicate its already established and probable future role in the chemotherapeutic armamentarium, they have served their intended purpose.

*Osteomyelitis.*—(Fig. 2.) *Type I* consists of circumscribed oval or circular areas of decreased density at the junction of metaphysis and diaphysis; *Type II*, of smaller areas of diminished density, usually seen in the shafts as slits or flat ellipses with the greatest axis parallel to that of the shaft; *Type III*, of bilaterally symmetrical areas of diminished density in the medial aspects of the proximal ends of the tibias, which erode the cortex immediately beneath the epiphyseal line (Wimberger's sign). These three were arbitrarily assigned grades of 2 in our scale. *Type IV*, fracture, may occur with any of the preceding, especially through *Type II*, and was indexed as grade 3. Although *Types I* and *II* may be encountered in acute pyogenic hematogenous osteomyelitis or multiple benign osseous tuberculosis,<sup>11</sup> they are also manifestations of fairly severe osseous syphilis. Whereas *Type III* may be pathognomonic of syphilis, it does not seem to appear more often in severe osseous syphilis than either *Types I* or *II*, and therefore received no greater weight. Although nonspecific, *Type IV* is associated with more extensive osteomyelitis and was weighted accordingly.

## OSTEOMYELITIS

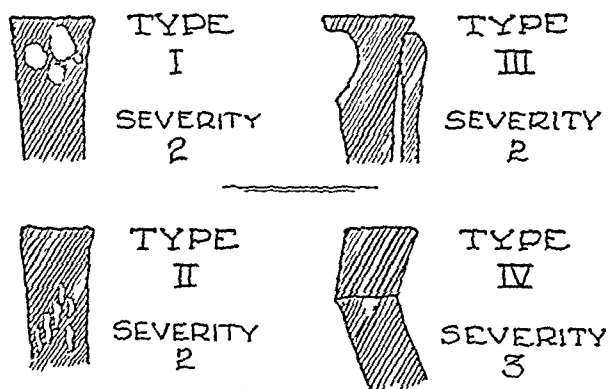


Fig. 2.—Diagrams to show types of osteomyelitis observed and severity assigned to each (see text).

*Periostitis.*—(Fig. 3.) *Type I* consists of a single line of periosteal elevation running nearly the length of the shaft but most pronounced near the middle; the underlying cortex and medulla usually appear normal. This type is encountered in many situations, as rapidly growing premature infants, malnutrition, traumatic periostitis of the newborn, and rickets.<sup>2, 5, 9, 11, 12</sup> Thus, a weight of only one was assigned. *Type II*, supportive and localized in nature, appears over cortical breaks or about regions of severe osteochondritis. For all practical purposes, it is very nearly identical with periosteal elevation seen with fractures, scurvy, osteomyelitis of pyogenic origin, or gonococcal periostitis.<sup>11</sup> Although relatively nonspecific, it is generally associated with more severe lesions and was given a weight of 2. *Type III*, essentially a multiplication

illness or injections of bismuth in the pregnant woman.<sup>2, 5, 8, 9, 10, 11</sup> Accordingly, a weight of one in our scale was assigned to this lesion. *Type II* is seen as a similar thickened transverse line of increased density but with a contiguous and shaftward transverse zone of diminished density. *Type II* may also be observed with disturbances in growth encountered in hemolytic lesions of the newborn, familial hemolytic anemia, bacteremia, and multiple birth injuries.<sup>5, 8, 11</sup> Thus, though relatively nonspecific, this lesion is presumably a more severe manifestation and was given a weight of 2. *Type III* appears as a deep zone of decreased density at the end of the shaft, with diminution or absence of the terminal shadow of increased density. It has also been associated with extremely rapid growth, congenital biliary atresia, injections of bismuth, and toxoplasmic encephalitis.<sup>5, 8, 11</sup> A weight of 2 was assigned to it. *Type IV* is almost certainly a reduplication of *Type II*, being composed of either doubled transverse

## OSTEOCHONDRITIS

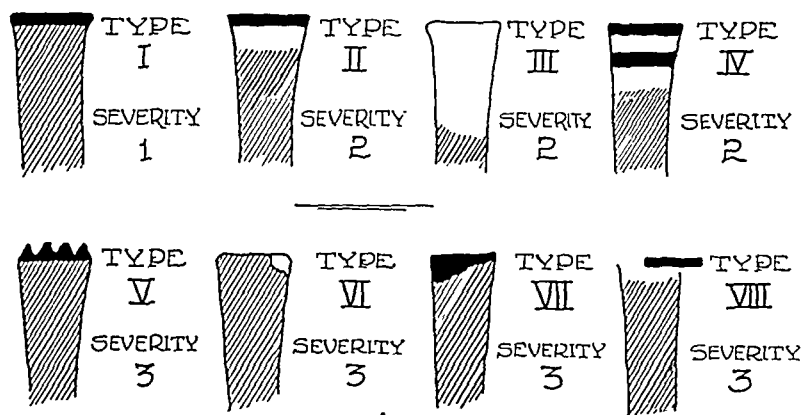


Fig. 1.—Diagrams to show types of osteochondritis observed and severity assigned to each (see text).

lines of increased density separated by a narrow band of diminished density or double alternating bands of increased and decreased density. Two widely separated periods of disturbances in growth or courses of bismuth injections can result in a similar appearance; it has also been seen in disseminated hematogenous tuberculosis.<sup>2, 8, 11</sup> Accordingly, a weight of 2 was assigned to this type. The remaining types of osteochondritis have been described only in osseous syphilis. Because of their specificity and also because the following types are usually seen only in the more severe forms of the disease, a grade of 3 was given to each: *Type V* is serration of the ends of the shafts, with "saw-toothed" metaphyses; *Type VI* is small foci of rarefaction or necrosis at the angle of the cartilage-shaft junction; *Type VII* is impaction through an area of osteochondritis; and *Type VIII* is horizontal displacement at the cartilage-shaft junction.

for comparison would consist of a large number of untreated syphilitic infants observed radiographically at two-week intervals from birth to 6 months of age, and at longer intervals thereafter. Furthermore, not only should the accurate date of maternal infection be known, but also the maternal syphilis should have been untreated. For many obvious reasons, such crucial conditions are impossible to attain. Consequently, our control data were derived from 134 roentgenographic observations of ninety-eight infants made before penicillin therapy was started. Discontinuous data of this sort are imperfect but are the best we have available. Factual information concerning date of maternal infection was too meager for analysis. Socioeconomic circumstances were such that less than one-half of the mothers of infants studied had received antisyphilitic therapy of any kind prior to delivery. Only a small minority had received therapy which might be considered "adequate" according to accepted standards. In ninety-four prepenicillin observations made during the first six months of life, treatment had been administered during pregnancy in twenty-eight and was satisfactory<sup>6</sup> for only five. Infantile osseous lesions were severe in three and moderate in two of these. Whereas final analysis of effects of inadequate maternal therapy must await the culmination of a larger sample, we doubt that subcutaneous amounts given the mother significantly influence the severity of lesions in the skeleton of her infant.

Tables I, II, III, and IV contain 134 roentgenologic observations in ninety-eight infants before treatment with penicillin. Combinations of osteochondritis, osteomyelitis, and periostitis (Table I) and the frequency of the various types of these (Tables II, III, and IV) are sufficiently obvious to require no further comment. An explanation is indicated at this point, however, concerning the estimation of severity. Suppose, for example, roentgenograms in an infant of 45 days disclosed osteochondritis of Types II and VII, osteomyelitis of Types I and III, and periostitis of Types I and II. By addition, the weight

TABLE I. PREPENICILLIN STATUS OF OSSEOUS CONGENITAL SYPHILIS IN NINETY EIGHT INFANTS

MANIFESTATIONS	DISTRIBUTION OF LESIONS BY MANIFESTATION AND AGE			
	AGE			
	1 90 DAYS	91 210 DAYS	211 365 DAYS	13 24 MONTHS
Number of children	43	33	16	20
Number of observations	54	40	19	21
Normal	0	0	2	5
Osteochondritis only	7	2	1	2
Osteomyelitis only	1	0	0	0
Periostitis only	1	8	11	10
Osteochondritis and osteomyelitis	1	0	0	0
Osteochondritis and periostitis	13	5	4	1
Osteomyelitis and periostitis	2	3	1	2
Osteochondritis, osteomyelitis, and periostitis	20	22	0	1
SEVERITY				
$\bar{V}$ *	6.739	6.550	2.995	2.524
S.D.	3.53	3.19	1.68	2.46
M.L.E.	3.56	3.23	1.73	2.32
S.E.	0.49	0.52	0.41	0.56

\*For explanation of symbols used in tables, see footnote in text.

of Type I, consists of onion-skin periosteal thickening, variously designated as ossifying periostitis, hypertrophic periostitis, or periostitis of Pehu. Whereas this type is relatively unusual and is sometimes encountered with diseases other than syphilis,<sup>13, 14, 15</sup> it appears later than Types I and II and is probably a late manifestation of healing. In spite of these considerations, because it appears severe, it was arbitrarily assigned a weight of 3. In *Type IV*, the shaft is widened and the cortex is thickened in the early stages. Because this represents a stage of nearly complete healing, the weight assigned was only one. *Type V* signifies a localized thickening of the anterior tibial cortex. Though it may occur in other bones, trauma probably explains this characteristic localization and persistence (saber shin). We believe it has the same significance and deserves the same weight as Type IV.

## PERIOSTITIS

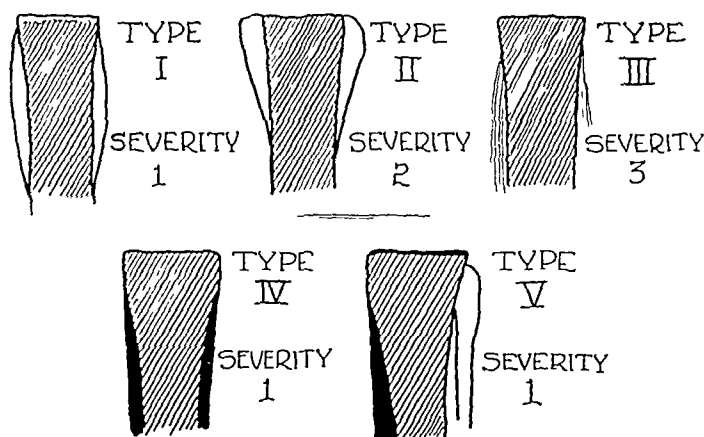


Fig. 3.—Diagrams to show types of periostitis observed and severity assigned to each (see text).

McLean<sup>13</sup> noted that the most common lesions developed in the first three months of life and considered those observed later to be residua or relapses. Data concerning such matters as the combinations of lesions, frequency of distribution in various bones, and variations with age, have been evaluated elsewhere<sup>13, 16, 17, 18</sup> and will not be worried further here. Just how much these osseous manifestations are influenced by associated vitamin deficiencies is difficult to determine. Certainly, pathologic evidence of rickets is far more common than radiographic,<sup>13</sup> and Levin<sup>19</sup> recently noted low levels for ascorbic acid in young syphilitic infants.\*

In order to analyze the effect of penicillin on the rate of healing, it is necessary to know the behavior of untreated osseous lesions. The ideal group

\*In only three infants of our series was the presence of either rickets or scurvy suggested by dietary history and clinical observations; characteristic roentgenographic evidence of these deficiencies, however, was lacking in all three. Chemical studies were not made routinely of vitamins C and D during and following treatment. These vitamins could conceivably have influenced rates of healing in a few.

for osteochondritis is 5, osteomyelitis 4, periostitis 3, and the total severity equals 12. By this method the average severity of pre- as well as postpenicillin osseous syphilis was graded.

Curves to show average severity of untreated osseous syphilis (Figs. 4 through 7) were obtained by smoothing average values within indicated age groups. Though only approximate, these illustrate a definitely changing severity with age. Modifications may be necessary when data are available for a larger number. Average total severity (Fig. 4) increases during the first three months, then declines relatively rapidly for three months, and more slowly thereafter. Osteochondritis and osteomyelitis rapidly increase in severity during the first 90 days, the former reaching its peak slightly earlier; they then subside to become relatively insignificant after 6 months of age and negligible after one year. Periostitis, on the other hand, increases in severity more slowly to its peak at about 6 months, then slowly declines.

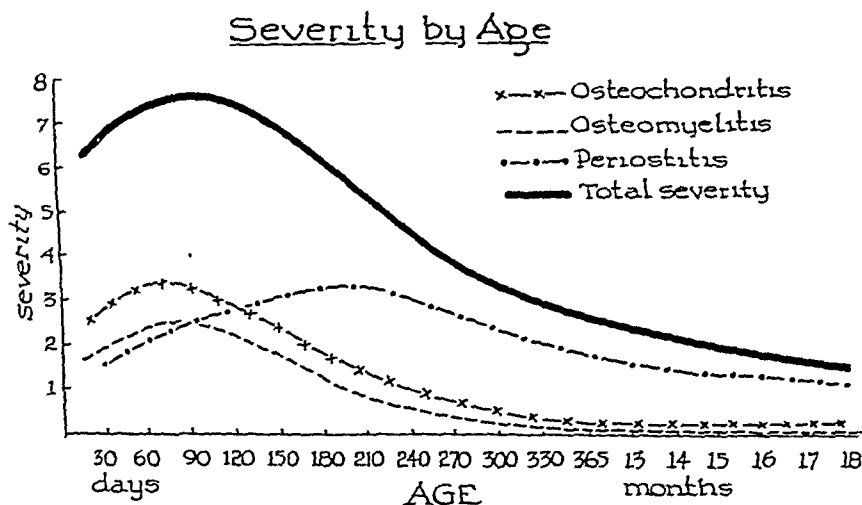


Fig. 4.—Empirically graded average severity of osseous lesions in ninety-eight untreated syphilitic infants (discontinuous observations, see Tables I to IV).

In Fig. 5 is indicated the total severity of untreated osseous syphilis where comparable serial gradings were possible. Reasons for occasional prolonged intervals without treatment need not concern us here. These individuals are contrasted with the curve of average total severity for age (see Fig. 4). It is noteworthy that the curve of average total severity reflects the fluctuations seen in serial observations. Particular attention should be paid to the extremely rapid increases in severity during the first 3 months of life. These fluctuations have been previously reported.<sup>20</sup>

Vogt<sup>21</sup> suggested that the high frequency of normal roentgenograms in syphilitic infants over one year of age may be related to survival of those with milder syphilis, and that the favorable late observations are biased by the higher fatality rate among infants with severe osseous syphilis. Whereas



TABLE II. PREFENICILLIN STATUS OF OSTEOCHONDRITIS IN NINETY-EIGHT INFANTS

TYPE	RELATION OF TYPE TO AGE			
	AGE			
	1-90 DAYS	91-210 DAYS	211-365 DAYS	13-24 MONTHS
Number of children	43	33	16	20
Number of observations	54	40	19	21
Absent	4	12	14	16
Type I	2	2	3	0
Type II	28	11	0	1
Type III	19	17	1	0
Type IV	1	2	1	2
Type V	11	4	0	1
Type VI	9	2	0	2
Type VII	1	3	0	0
Type VIII	3	1	0	0
SEVERITY				
$\bar{x}$	3.148	2.200	0.368	0.714
S.D. $_{\bar{x}}$	2.06	1.98	0.67	1.39
M.L.E.	2.08	2.01	0.69	1.42
S.E. $_{\bar{x}}$	0.28	0.32	0.16	0.32

TABLE III. PREFENICILLIN STATUS OF OSTEOMYELITIS IN NINETY-EIGHT INFANTS

TYPE	RELATION OF TYPE TO AGE			
	AGE			
	1-90 DAYS	91-210 DAYS	211-365 DAYS	13-24 MONTHS
Number of children	43	33	16	20
Number of observations	54	40	19	21
Absent	21	15	18	18
Type I	15	13	0	1
Type II	13	12	0	2
Type III	15	14	0	0
Type IV	7	2	1	0
SEVERITY				
$\bar{x}$	1.981	2.025	0.158	0.286
S.D. $_{\bar{x}}$	1.96	1.97	0.47	0.88
M.L.E.	1.98	2.00	0.48	0.90
S.E. $_{\bar{x}}$	0.27	0.32	0.11	0.20

TABLE IV. PREFENICILLIN STATUS OF PERIOSTITIS IN NINETY-EIGHT INFANTS

TYPE	RELATION OF TYPE TO AGE			
	AGE			
	1-90 DAYS	91-210 DAYS	211-365 DAYS	13-24 MONTHS
Number of children	43	33	16	20
Number of observations	54	40	19	21
Absent	10	2	3	8
Type I	35	28	4	4
Type II	22	7	1	1
Type III	1	16	8	5
Type IV	0	3	9	11
Type V	0	0	0	1
SEVERITY				
$\bar{x}$	1.611	2.325	2.368	1.524
S.D. $_{\bar{x}}$	1.21	1.42	1.50	1.65
M.L.E.	1.22	1.44	1.54	1.69
S.E. $_{\bar{x}}$	0.17	0.23	0.36	0.38

infants with clinically severe congenital syphilis often have severe osseous lesions,<sup>20</sup> serial observations (Fig. 5) indicate that even without treatment these heal along a fairly orderly time pattern. For the present, correction of control observations for expected fatality rates is not possible.

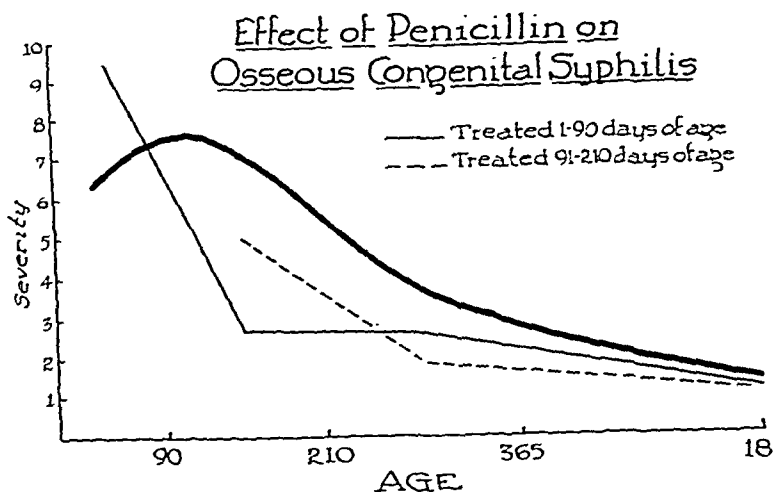


Fig. 7.—Average total severity, treated and untreated (see Tables I, V, and IX).

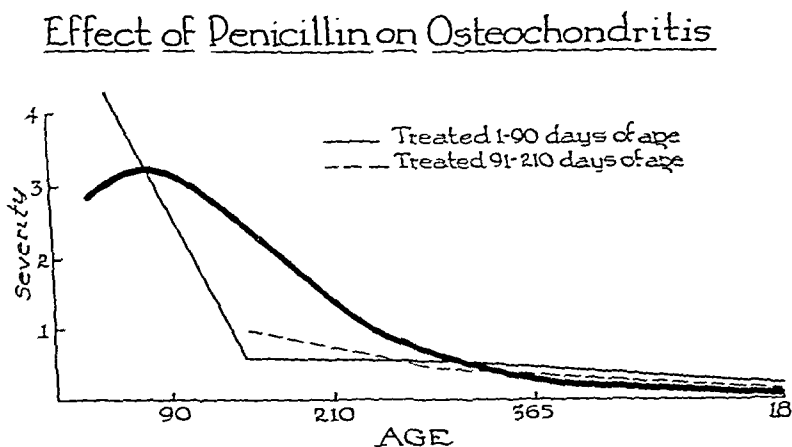


Fig. 8.—Average severity of osteochondritis, treated and untreated (see Tables II, VI, and X).

There have been few reports<sup>10, 21, 22</sup> concerning effects of antisyphilitic therapy upon osseous lesions; comparison between rates of healing of untreated and treated osseous syphilis has not been made. The clinical material, of which this study comprises a part, the dosage schedules employed, and clinical and serologic results of treatment with penicillin have been reported elsewhere.<sup>23, 24, 25</sup> No attempt is made here to correlate rate of healing with particular dosage schedules of penicillin. The small number of patients treated with similar schedules in each age group precludes their comparison.

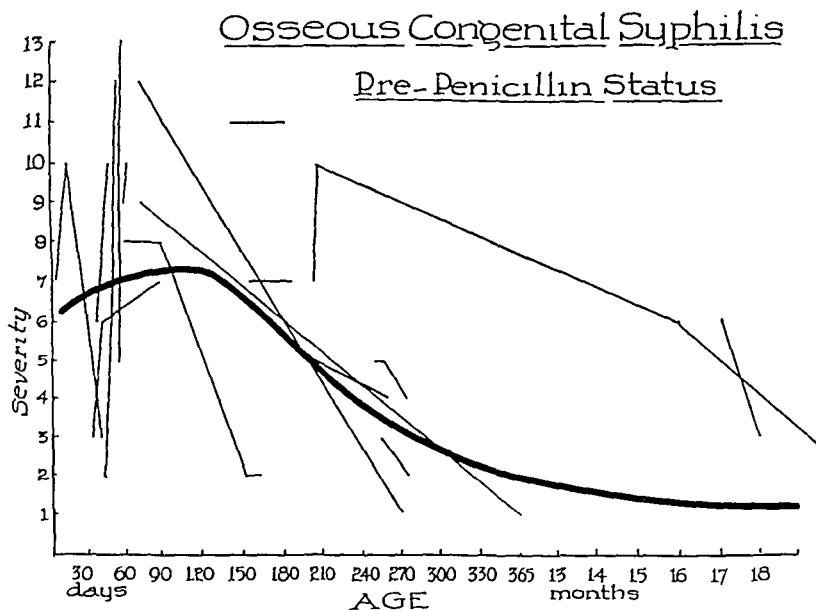


Fig. 5.—Serial observations for sixteen infants contrasted with smoothed curve of average total severity; all untreated.

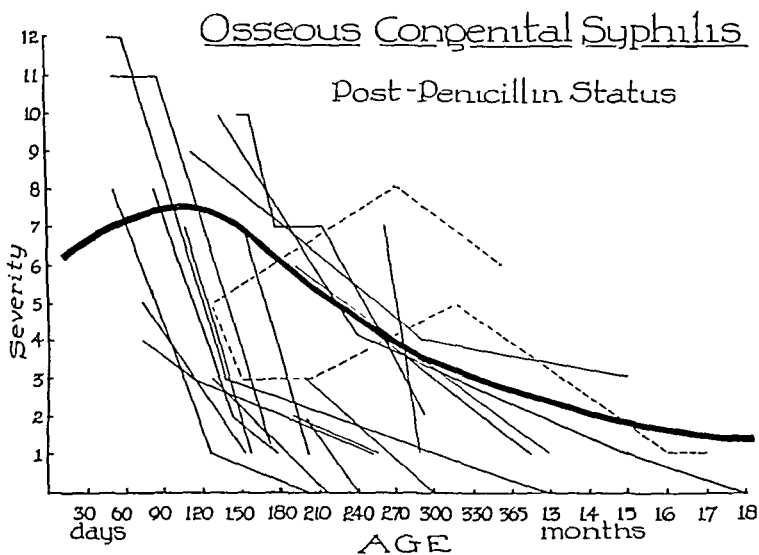


Fig. 6.—Serial observations for twenty infants following penicillin therapy contrasted with curve of average total severity for those untreated. Dotted lines indicate status of osseous lesions in two infants who relapsed clinically.

be the basis for comparison. Intervals were selected by inspection of the curve for total severity of untreated lesions: one to 90 days of age represents the period of increasing severity, 91 to 210 days that of rapidly decreasing severity, 211 to 365 days that of moderate decline, and 13 to 24 months that of slow decline. Unfortunately, adequate roentgenographic observations were available only for those infants treated during the first two of these periods (Tables V through XII). Techniques\* adapted for analysis of small samples were employed, and the means of corresponding age groups in treated and untreated infants were compared by obtaining the relative deviate (k) between the means. Because the numbers involved are small, only high values of k were considered significant; a value of k greater than 3.5 indicates a probability of less than 5 out of 10,000 that an observed difference between the means would be due to errors in random sampling.

TABLE V. POSTPENICILLIN STATUS OF OSSEOUS CONGENITAL SYPHILIS IN TWENTY-EIGHT INFANTS TREATED AT 1 TO 90 DAYS OF AGE

MANIFESTATIONS	DISTRIBUTION OF LESIONS BY MANIFESTATION AND AGE			
	AGE			
	1-90 DAYS	91-210 DAYS	211-365 DAYS	13-24 MONTHS
Number of children	11	19	12	4
Number of observations	13	25	13	6
Normal	0	4	3	2
Osteochondritis only	0	0	2	1
Osteomyelitis only	0	0	0	0
Periostitis only	0	10	5	3
Osteochondritis and osteomyelitis	0	0	0	0
Osteochondritis and periostitis	1	4	2	0
Osteomyelitis and periostitis	0	4	0	0
Osteochondritis, osteomyelitis and periostitis	12	3	1	0

SEVERITY				
$\bar{x}$	9.462	2.680	2.462	1.667
S.D. <sub>x</sub>	3.18	2.59	2.65	0.62
M.L.E.	3.31	2.64	2.76	0.68
S.E. <sub><math>\bar{x}</math></sub>	0.96	0.54	0.80	0.30
k	0.25	5.18	0.48	1.34
Significance	none	high	none	none

$$\text{*Mean } (\bar{x}) = \frac{\sum x}{N}$$

$$\text{Standard Deviation (S.D.)}_x = \sqrt{\frac{\sum x^2}{N} - \bar{x}^2}$$

$$\text{Maximum likelihood estimate of standard deviation (M.L.E.)} = \text{S.D.}_x \sqrt{\frac{N}{N-1}}$$

$$\text{Standard error of the mean (S.E.)}_x = \frac{\text{S.D.}_x}{\sqrt{N-1}}$$

$$\text{Relative deviate between the means (k)} = \frac{\bar{x} - \bar{y}}{\sqrt{\text{S.E. } \bar{x}^2 + \text{S.E. } \bar{y}^2}}$$

Values of k > 1.96 (P < 0.05), questionably significant.

Values of k > 2.80 (P < 0.005), probably significant.

Values of k > 3.5 (P < 0.0005), highly significant.

Serial examinations following treatment (Fig. 6) were contrasted with the average total severity derived for those untreated. These few observations indicate that healing is rapid in infants treated during the first three months of life, but slow in those treated later. Figs. 7, 8, 9, and 10 portray average

### Effect of Penicillin on Osteomyelitis

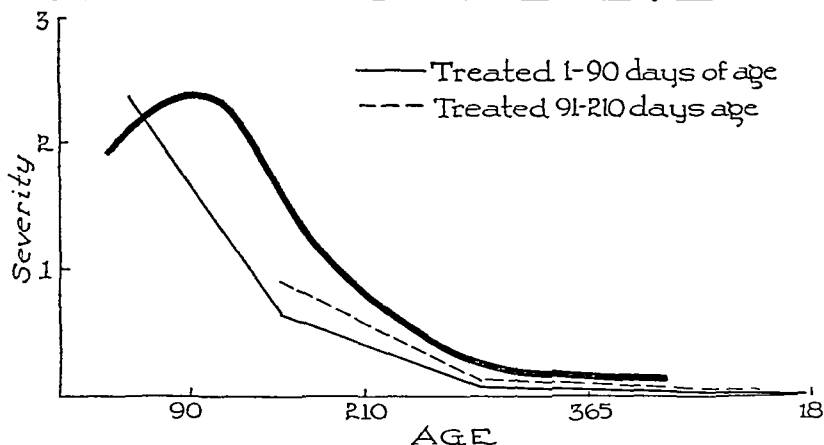


Fig. 9.—Average severity of osteomyelitis, treated and untreated (see Tables III, VII, and XI).

### Effect of Penicillin on Periostitis

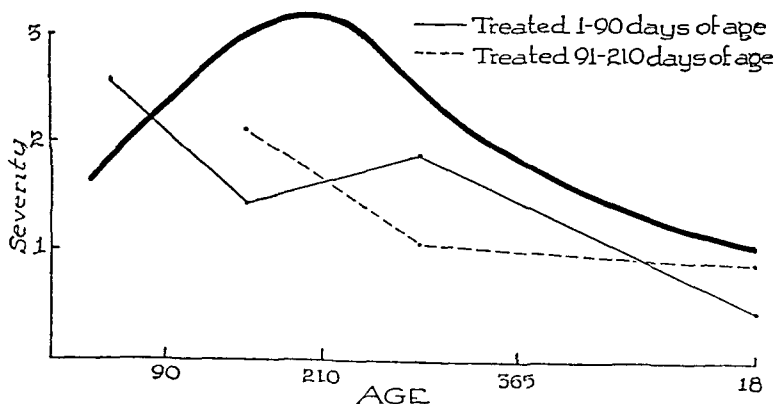


Fig. 10.—Average severity of periostitis, treated and untreated (see Tables IV, VIII, and XII).

severities following treatment with penicillin for two groups, those treated before 90 days of age and those treated during the next four months. Included for comparative purposes are smoothed curves to show average severity of untreated osseous syphilis and its separate manifestations.

Statistical analysis is required to ascertain whether these observed differences in rates of healing are significant. Since age is the major factor, it must

be the basis for comparison. Intervals were selected by inspection of the curve for total severity of untreated lesions: one to 90 days of age represents the period of increasing severity, 91 to 210 days that of rapidly decreasing severity, 211 to 365 days that of moderate decline, and 13 to 24 months that of slow decline. Unfortunately, adequate roentgenographic observations were available only for those infants treated during the first two of these periods (Tables V through XII). Techniques\* adapted for analysis of small samples were employed, and the means of corresponding age groups in treated and untreated infants were compared by obtaining the relative deviate (k) between the means. Because the numbers involved are small, only high values of k were considered significant; a value of k greater than 3.5 indicates a probability of less than 5 out of 10,000 that an observed difference between the means would be due to errors in random sampling.

TABLE V. POSTPENICILLIN STATUS OF OSSEOUS CONGENITAL SYPHILIS IN TWENTY-EIGHT INFANTS TREATED AT 1 TO 90 DAYS OF AGE

MANIFESTATIONS	DISTRIBUTION OF LESIONS BY MANIFESTATION AND AGE			
	AGE			
	1-90 DAYS	91-210 DAYS	211-365 DAYS	13-24 MONTHS
Number of children	11	19	12	4
Number of observations	13	25	13	6
Normal	0	4	3	2
Osteochondritis only	0	0	2	1
Osteomyelitis only	0	0	0	0
Periostitis only	0	10	5	3
Osteochondritis and osteomyelitis	0	0	0	0
Osteochondritis and periostitis	1	4	2	0
Osteomyelitis and periostitis	0	4	0	0
Osteochondritis, osteomyelitis and periostitis	12	3	1	0

SEVERITY				
$\bar{x}$	9.462	2.680	2.462	1.667
S.D. <sub>x</sub>	3.18	2.59	2.65	0.62
M.L.E.	3.31	2.64	2.76	0.68
S.E. <sub><math>\bar{x}</math></sub>	0.96	0.54	0.80	0.30
k	0.25	5.18	0.48	1.34
Significance	none	high	none	none

$$\text{*Mean } (\bar{x}) = \frac{\sum x}{N}$$

$$\text{Standard Deviation (S.D.)} = \sqrt{\frac{\sum x^2}{N} - \bar{x}^2}$$

$$\text{Maximum likelihood estimate of standard deviation (M.L.E.)} = \text{S.D.} \sqrt{\frac{N}{N-1}}$$

$$\text{Standard error of the mean (S.E.)} = \frac{\text{S.D.}}{\sqrt{N-1}}$$

$$\text{Relative deviate between the means (k)} = \frac{\bar{x} - \bar{y}}{\sqrt{\text{S.E. } \bar{x}^2 + \text{S.E. } \bar{y}^2}}$$

Values of k > 1.96 (P < 0.05), questionably significant.

Values of k > 2.50 (P < 0.005), probably significant.

Values of k > 3.5 (P < 0.0005), highly significant.

TABLE VI. POSTPENICILLIN STATUS OF OSTEOCHONDritis IN TWENTY-EIGHT INFANTS TREATED AT 1 TO 90 DAYS OF AGE

TYPE	RELATION OF TYPE TO AGE			
	AGE			
	1-90 DAYS	91-210 DAYS	211-365 DAYS	13-24 MONTHS
Number of children	11	19	12	4
Number of observations	13	25	13	6
Absent	0	18	8	5
Type I	3	1	3	1
Type II	6	1	0	0
Type III	1	5	0	0
Type IV	3	0	1	0
Type V	3	1	1	0
Type VI	3	0	0	0
Type VII	3	0	0	0
Type VIII	2	0	0	0
SEVERITY				
$\bar{x}$	4.308	0.640	0.615	0.167
S.D. $_{\bar{x}}$	2.61	1.20	0.92	0.37
M.L.E.	2.72	1.22	0.96	0.41
S.E. $_{\bar{x}}$	0.78	0.25	0.28	0.18
k	1.39	3.83	0.77	1.49
Significance	none	high	none	none

TABLE VII. POSTPENICILLIN STATUS OF OSTEOMYELITIS IN TWENTY-EIGHT INFANTS TREATED AT 1 TO 90 DAYS OF AGE

TYPE	RELATION OF TYPE TO AGE			
	AGE			
	1-90 DAYS	91-210 DAYS	211-365 DAYS	13-24 MONTHS
Number of children	11	19	12	4
Number of observations	13	25	13	6
Absent	1	18	12	6
Type I	6	2	1	0
Type II	3	1	0	0
Type III	5	4	0	0
Type IV	2	1	0	0
SEVERITY				
$\bar{x}$	2.615	0.680	0.154	0.00
S.D. $_{\bar{x}}$	1.27	0.58	0.54	0.00
M.L.E.	1.32	0.59	0.56	0.00
S.E. $_{\bar{x}}$	0.38	0.12	0.16	0.00
k	1.35	3.93	0.02	1.45
Significance	none	high	none	none

This analysis reveals no significant difference in rates of healing for treated and untreated groups unless therapy is given before the age of 3 months. Significant acceleration continuing for about four months after such early treatment is largely due to improvements in osteochondritis and osteomyelitis. A similar difference of only probable significance occurs for periostitis. After seven months, differences in rates of healing are not significant. Therapy administered in the interval between 3 to 7 months caused no significant acceleration.

Serial roentgenograms were obtained in thirty-four infants during or shortly after treatment with penicillin: a temporary increase in severity was observed four times (Table XIII), each within the first 3 months of life. As noted previously, rapid fluctuations of untreated osseous lesions characterize this early age, the period of exacerbation. Inasmuch as there is also a lag in improvement after therapy given at this age, it seems probable that penicillin is not responsible for this phenomenon. Indeed, it is remarkable that exacerbations were not more common among these youngest infants. One possible explanation for these has been given by Levin,<sup>19</sup> who noted a fall in levels for ascorbic acid during intensive arsenical therapy administered in the first 6 months of life. The degree to which this affects healing remains conjectural.

TABLE VIII. POSTPENICILLIN STATUS OF PERIOSTITIS IN TWENTY-EIGHT INFANTS TREATED AT 1 TO 90 DAYS OF AGE

TYPE	RELATION OF TYPE TO AGE			
	AGE			
	1-90 DAYS	91-210 DAYS	211-365 DAYS	13-24 MONTHS
Number of children	11	19	12	4
Number of observations	13	25	13	6
Absent	0	4	5	3
Type I	13	14	2	0
Type II	7	1	0	0
Type III	2	3	4	1
Type IV	0	9	8	3
Type V	0	0	1	0
SEVERITY				
$\bar{x}$	2.538	1.360	1.769	1.000
S.D. <sub>x</sub>	1.08	1.20	1.93	1.41
M.L.E.	1.12	1.22	2.01	1.54
S.E. <sub><math>\bar{x}</math></sub>	0.32	0.25	0.58	0.69
k	2.55	2.84	0.86	0.67
Significance	questionable	probable	none	none

TABLE IX. POSTPENICILLIN STATUS OF OSSEOUS CONGENITAL SYPHILIS IN TWENTY-TWO INFANTS TREATED AT 91 TO 210 DAYS OF AGE

MANIFESTATIONS	DISTRIBUTION OF LESIONS BY MANIFESTATION AND AGE		
	AGE		
	91-210 DAYS	211-365 DAYS	13-24 MONTHS
Number of children	10	14	7
Number of observations	14	17	8
Normal	0	5	2
Osteochondritis only	0	3	0
Osteomyelitis only	0	0	0
Periostitis only	7	6	5
Osteochondritis and osteomyelitis	0	0	0
Osteochondritis and periostitis	2	1	1
Osteomyelitis and periostitis	0	1	0
Osteochondritis, osteomyelitis, and periostitis	5	1	0
SEVERITY			
$\bar{x}$	4.929	1.882	1.000
S.D. <sub>x</sub>	3.37	2.30	0.39
M.L.E.	3.50	2.37	0.42
S.E. <sub><math>\bar{x}</math></sub>	0.97	0.59	0.16
k	1.47	1.41	2.60
Significance	none	none	questionable



TABLE X. POSTPENICILLIN STATUS OF OSTEOCHONDRITIS IN TWENTY-TWO INFANTS TREATED AT 91 TO 210 DAYS OF AGE

RELATION OF TYPE TO AGE			
TYPE	AGE		
	91-210 DAYS	211-365 DAYS	13-24 MONTHS
Number of children	10	14	7
Number of observations	14	17	8
Absent	7	12	7
Type I	0	2	1
Type II	3	0	0
Type III	1	1	0
Type IV	3	1	0
Type V	0	1	0
Type VI	0	0	0
Type VII	0	0	0
Type VIII	0	0	0
SEVERITY			
$\bar{x}$	1.000	0.529	0.125
S.D. <sub>x</sub>	1.0	0.92	0.33
M.L.E.	1.04	0.95	0.35
S.E. <sub>x</sub>	0.29	0.24	0.13
k	2.78	0.56	1.71
Significance	questionable	none	none

TABLE XI. POSTPENICILLIN STATUS OF OSTEOMYELITIS IN TWENTY-TWO INFANTS TREATED AT 91 TO 210 DAYS OF AGE

RELATION OF TYPE TO AGE			
TYPE	AGE		
	91-210 DAYS	211-365 DAYS	13-24 MONTHS
Number of children	10	14	7
Number of observations	14	17	8
Absent	9	15	8
Type I	0	0	0
Type II	4	2	0
Type III	5	0	0
Type IV	2	0	0
SEVERITY			
$\bar{x}$	1.714	0.235	0.00
S.D. <sub>x</sub>	0.26	0.64	0.00
M.L.E.	0.27	0.66	0.00
S.E. <sub>x</sub>	0.07	0.16	0.00
k	0.95	0.39	1.45
Significance	none	none	none

Pseudoparalysis, present at the initiation of treatment in fifteen infants, was known to have disappeared within three weeks in twelve; all had cleared within one month. In satisfactory roentgenograms of affected extremities for twelve, osteochondritis and periostitis were invariably present, osteomyelitis was noted eight times, no specific type (Figs. 1, 2, and 3) was common to all, there were no fractures, and empirically graded severity ranged from 4 to 16. Films of eight of these infants were compared with others taken at the time pseudoparalysis disappeared; severity had increased in three, decreased in four, and remained unchanged in one.

The validity of our observations depends on the following assumptions: (1) discontinuous estimates of severity in untreated osseous syphilis constitute adequate control material; (2) grossly inadequate treatment of the pregnant woman does not significantly alter the character of infantile osseous syphilis; (3) differences in osseous syphilis due to various dosages of penicillin employed in our study are unimportant. Testing of these assumptions must await opportunity to study a much larger number of patients.

TABLE XII. POSTPENICILLIN STATUS OF PERIOSTITIS IN TWENTY-TWO INFANTS TREATED AT 91 TO 210 DAYS OF AGE

TYPE	RELATION OF TYPE TO AGE		
	AGE		
	91-210 DAYS	211-365 DAYS	13-24 MONTHS
Number of children	10	14	7
Number of observations	14	17	8
Absent	0	8	2
Type I	8	1	0
Type II	0	1	0
Type III	6	3	0
Type IV	5	7	6
Type V	0	0	1
SEVERITY			
$\bar{x}$	2.214	1.118	0.875
S.D. <sub>x</sub>	1.21	1.41	0.60
M.L.E.	1.26	1.45	0.64
S.E. <sub><math>\bar{x}</math></sub>	0.35	0.36	0.24
k	0.27	2.44	1.45
Significance	none	questionable	none

TABLE XIII. STATUS OF OSSEOUS SYPHILIS IMMEDIATELY FOLLOWING PENICILLIN THERAPY\*

AGE AT START OF PENICILLIN	INTERVAL AFTER START OF PENICILLIN (DAYS)	STATUS OF OSSEOUS LESIONS AT INDICATED INTERVAL			NO. INFANTS
		WORSE	NOTE CHANGE	IMPROVED	
1-90 days	1-15	3	4	2	9
	16-30	-	1	1	2
	31-45	1	1	2	4
	46-60	-	1	3	4
		<u>4</u>	<u>7</u>	<u>8</u>	<u>19</u>
91-210 days	1-15		3	-	3
	16-30		1	3	4
	46-60		-	3	3
			<u>4</u>	<u>6</u>	<u>10</u>
211-365 days	41-60		-	2	2
13-24 months	31-45		-	1	1
	46-60		1	1	2
			<u>1</u>	<u>2</u>	<u>3</u>

\*The number of days between the last prepenicillin roentgenogram and start of penicillin therapy was less than four in sixteen infants, less than eight in ten, less than eleven in three, and less than fifteen in five.

## CONCLUSIONS

1. The behavior of osseous congenital syphilis in untreated infants follows a fairly definite pattern of rapidly increasing severity during the first 3 months

of life and slow healing thereafter. Improvement results from decreasing severity of osteomyelitis and osteochondritis, periosteal changes increase in prominence over a longer period and persist as the commonest residua. The course of a given lesion in any individual patient cannot be accurately predicted.

2 Dosages of penicillin employed so far have temporarily accelerated healing of osseous syphilis only in infants treated during the first three months of life. This acceleration, as in untreated controls, occurs principally in osteochondritis and osteomyelitis, simultaneous improvement in periostitis is only of probable significance. No such significant effects were observed among those treated during the next four months. The mode of healing for any particular type of lesion, as herein described, has not been evaluated.

3 Increase in severity of these lesions during or shortly after penicillin therapy occurs in an age group where this phenomenon is to be expected without treatment.

4 Pseudoparalysis disappears without any specific changes in the roentgenograms, indeed, osseous lesions may even appear worse after pseudoparalysis subsides.

#### ADDENDUM

To determine whether arbitrary changes in weighted severity would alter these conclusions, data were reanalyzed as follows: The weight of types III and IV was increased to 3, that of types V and VI to 10, and of types VII and VIII to 5. Osteomyelitis of type III was increased to 10, and of type IV reduced to 2. Periostitis, type III, was also reduced to 2. An increased value was thus placed on lesions commonly considered to be more specific for syphilis. If penicillin affects osseous syphilis, this maneuver should accentuate any difference between treated and untreated groups, but actually the observed discrepancy was only slight. A highly significant difference appeared only in the total severity of the group treated in the first three months of life and observed at 91 to 210 days of age. No other differences were of more than probable significance. In the group treated during the first three months of life, the latter differences appeared in osteochondritis observed at 91 to 210 days of age and in periostitis observed at one to 90 and 91 to 210 days of age. In infants treated from the third to seventh month of life a difference of only probable significance also occurred in osteochondritis observed at 91 to 210 days. Under the conditions of this study it would seem doubtful, therefore, that penicillin effected more than a transitory increase in the rate of healing of osseous syphilis in those infants treated under 90 days.

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## CELIAC SYNDROME

### VI. THE RELATIONSHIP OF CELIAC DISEASE, STARCH INTOLERANCE, AND STLATORRHEA

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FOR some years my co-workers and I have been studying chronic malnutrition and chronic indigestion in infants and children, with especial reference to those patients presenting the celiac syndrome. One object of this project has been to find means of separating these cases into groups on the basis of etiology and pathogenesis, with the hope that informed therapy might be more consistently effective than the trial-and-error methods which have been necessary in the past. In somewhat less than one-half of the cases a satisfactory morphologic or bacteriologic explanation has been found, for example: fibrocystic disease of the pancreas, stenosis of the ileum, or chronic enteric infection due to *Ascaris*, *Giardia* or *Salmonella*. The cases in which no anatomic or bacteriologic basis for the disease has been found, however, form the major portion of our series. This is a preliminary report on the observations on the latter "idiopathic" group, which is referred to as the group of patients with celiac disease. This report represents a summary of the present status of the investigation, and an incomplete report of the data on which our concept of celiac disease is based. The remaining evidence on the technical details will be reported later.

The term celiac disease, as used in this paper, is applied to those patients who have chronic or recurrent diarrhea some time between the sixth month and sixth year, without demonstrable bacteriologic or anatomic basis, and who are intolerant of a normal diet for their age, respond to dietary therapy, and at some time in their course have a protuberant abdomen and a slow gain in weight. For reasons to be given later, the presence of steatorrhea has not been required for the diagnosis of celiac disease. The data to be presented were obtained from eighty-three patients who fulfilled these criteria and in whom both assay of pancreatic enzymes in the duodenal juice and chemical analysis of feces for fat were done. Cases of fibrocystic disease of the pancreas were excluded on the basis of failure to demonstrate normal levels of trypsin in the duodenal juice, a criterion which previous experience has shown to be reliable. The cases differed in severity, but all were sufficiently severe for hospitalization.

First to be considered is the course of the disease in the more severe cases, with an illustrative example.

R. T., a girl, was admitted to Babies Hospital at the age of 22 months in a severe state of malnutrition and with a weight of 12 pounds. At birth she had appeared normal and vigorous. Beginning in the neonatal period, however, there were bouts of diarrhea lasting

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from four to six weeks and recurring every two or three months. These episodes began with a respiratory infection and fever, promptly followed by watery diarrhea with from ten to fifteen stools a day. After a week or more the diarrhea gradually decreased in severity, the stools became large, pale, and pasty, and after a month or so numbered one to two daily. After a respite of a month or more, the cycle repeated itself. At about 12 months of age the abdomen was observed to be large. Her appetite had been poor and gain was slow, with a peak weight of 14 pounds at 14 months. Her development was delayed:

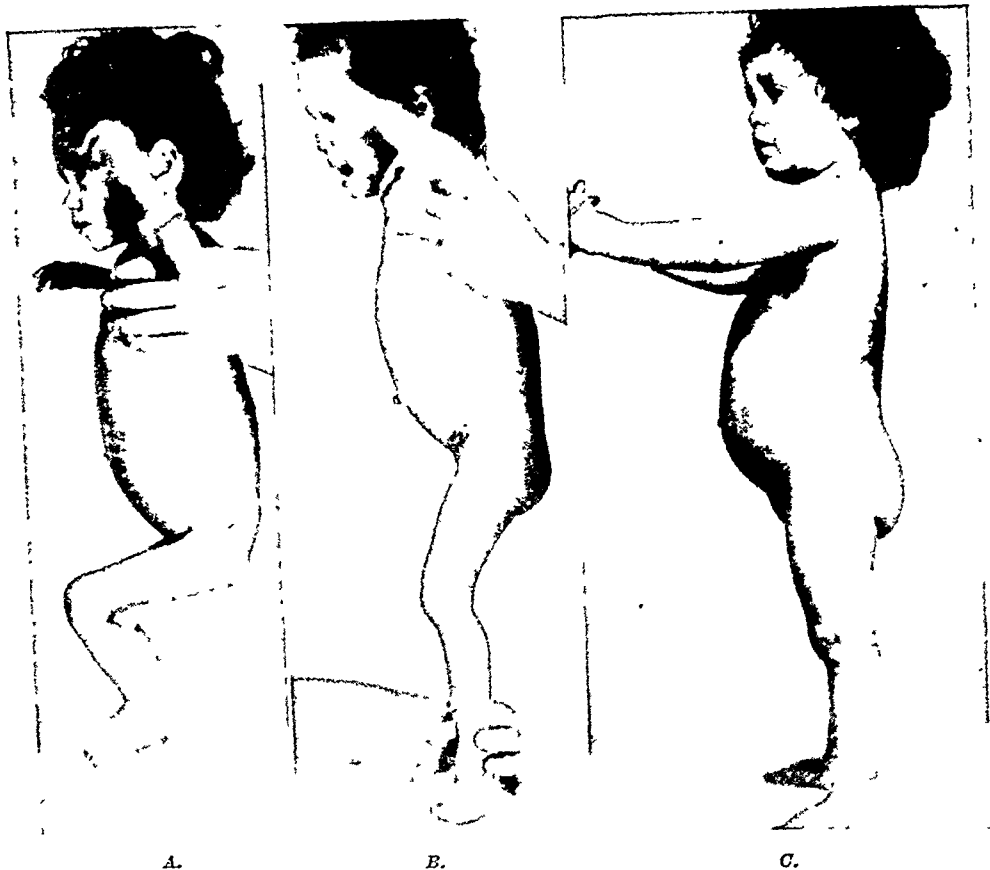


Fig. 1.—R. T. A, On admission, at 22 months of age. B, At 24 months of age. C, At 3 years.

she sat alone at 14 months. Her first teeth appeared at 18 months and she had never stood alone. A variety of diets had proved unsuccessful. For the eight months prior to her admission she had been in another hospital where she had received parenteral fluids during the acute episodes and parenteral therapy with vitamin B complex and liver concentrates without benefit. Her diet had consisted of a formula of evaporated milk, rice flour and water, and cereals. Because of her failure to respond to parenteral vitamin therapy, the diagnosis of celiac disease was questioned. However, the response to a modified diet in association with vitamin therapy was prompt and continued (Figs. 1 and 2). The two dips in her later weight curve correspond to brief periods of large foul stools following respiratory infections. Her progress has been otherwise uneventful. She is still on a modified diet.

The course of this patient consists of three periods: (1) a prodromal period during which there were bouts of diarrhea associated with upper respiratory

infections, with the first episode occurring during the first month of life; (2) a critical period starting at about one year of age, with loss of weight and the physical appearance associated with celiac disease; this continued for about one year until the institution of appropriate dietary therapy; and (3) a prolonged maintenance period during which the child was well while she remained on a modified diet but had several relapses when the regime was made more liberal.

Analysis of our series of eighty-three cases shows that the symptoms of indigestion, usually with diarrhea predominating, began before the age of 6 months in about one-third of the cases, between 6 and 12 months in another third, and between one and 3 years in the remainder. The diet and supplements prior to the onset of diarrhea were adequate in nearly every case, and the onset of the disease was insidious. The manner of onset varied. In some instances the stools were observed to be usually large but not watery prior to the first bout of diarrhea; sometimes the child had several bouts of diarrhea and then refused feedings, ceased to have diarrhea, and lost weight. In the majority of cases the episodes of diarrhea began with an upper respiratory infection, often a mild one.

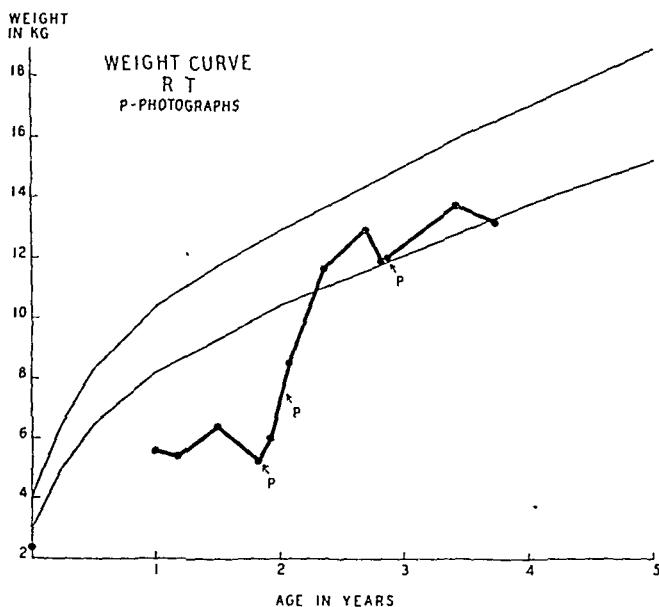


Fig. 2.—Weight curve for R. T. showing response to therapy and the times at which the photographs of Fig. 1 were taken.

The critical period sometimes followed a rapid succession of such respiratory infections associated with diarrhea, and not infrequently it has followed the introduction of a restricted bland diet designed to control the diarrhea. In several cases the diarrhea has become uncontrollable after some weeks or months of an elimination diet given in the belief that the symptoms were due to food allergy. Occasionally the classical picture of severe celiac disease develops without apparent precipitating factors. Usually, however, the precipitating factors are

of a kind which might be expected to lead to nutritional deficiency. Most of the symptoms of the critical period disappear with remarkable and gratifying rapidity with appropriate dietary and vitamin therapy. The evidence is strong that the critical period represents a multiple deficiency state which is almost always reversible, with the present knowledge of vitamins. In the present series



FIG. 3.—R. F., aged 11 months.

there has been one fatality among the thirty-seven cases which showed the classical symptoms in severe degree. We may learn of the course of the patients who have been inadequately treated from the reports that antedate the knowledge of vitamins such as the classical ones of Gee,<sup>1</sup> Herter,<sup>2</sup> and Fanconi.<sup>3</sup> In 1939 Hardwick<sup>4</sup> summarized the data on mortality. From his figures an average mortality of 15 per cent is calculated, the majority of the deaths occurring in the second and third years. Many of the survivors ran a chronic course and were ultimately dwarfed and sometimes deformed (Parsons<sup>5</sup>). The low mortality and excellent recovery of the present series is in contrast.

The maintenance phase of the disease is prolonged. For the first year or so after the normal weight is recovered the patients may continue to have brief recurrences of diarrhea precipitated either by a respiratory infection or by a



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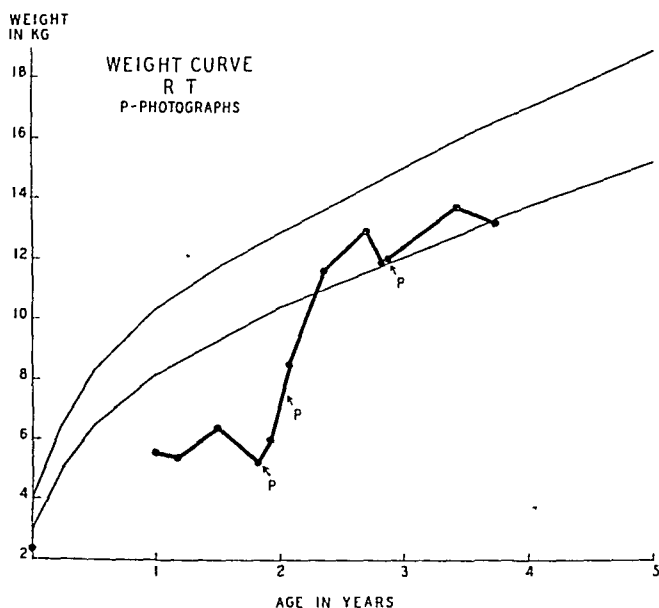


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The maintenance phase of the disease is prolonged. For the first year or so after the normal weight is recovered the patients may continue to have brief recurrences of diarrhea precipitated either by a respiratory infection or by a

break in diet. After an interval of one to several years it is possible to relax the dietary restrictions somewhat without ill effect, and by school age these restrictions can usually be mild. My personal experience does not as yet go further. Late recurrences, even in adult life, have been observed, and these may respond less readily to treatment.

The general pattern of the disease in different patients shows an almost monotonous uniformity, with some variation in the age at which the critical period manifests itself. The weight curves and serial photographs of several patients are shown to emphasize this point. It is of interest that the patients with crisis before the first year do not show as striking a change in body contours as do those who have experienced a longer prodromal period and an onset of the critical period after the age of 18 months. (Compare Figs. 3, 5, and 7.)

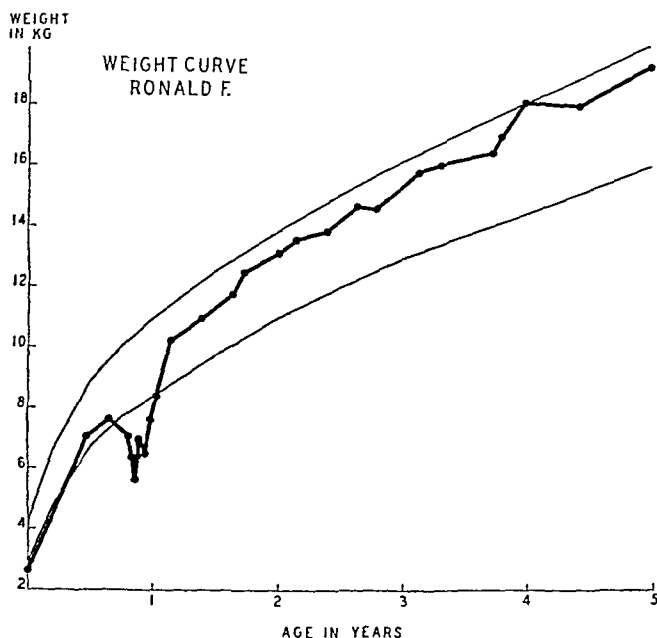


Fig. 4.—Weight curve of R. F., given as an example of the course of patients with the critical period during the first year of life.

It would appear, from the course of the disease, that the critical period constitutes a multiple deficiency syndrome superimposed upon a constitutional defect, and bears to this defect a relationship comparable to that which diabetic coma bears to diabetes. If this be true, as I believe it is, it becomes important to distinguish the clinical and laboratory findings which are the result of nutritional deficiency from those which are a part of the basic process. The two criteria available to us are: (1) the recognition of changes known to be due to the deficiency of a specific substance, for example, scurvy, rickets, keratomalacia, cheilosis, hypoprothrombinemia, and macrocytic anemia, any of which may be encountered occasionally in celiac disease; (2) demonstration that phenomena

as yet not known to be the result of the lack of a specific substance are transitory and respond to a diet containing foods known to be good sources of a variety of nutritional substances. The residual phenomena which are consistently found both early in the course of the disease and also after the child has regained normal weight and activity may tentatively be considered as part of the basic process.

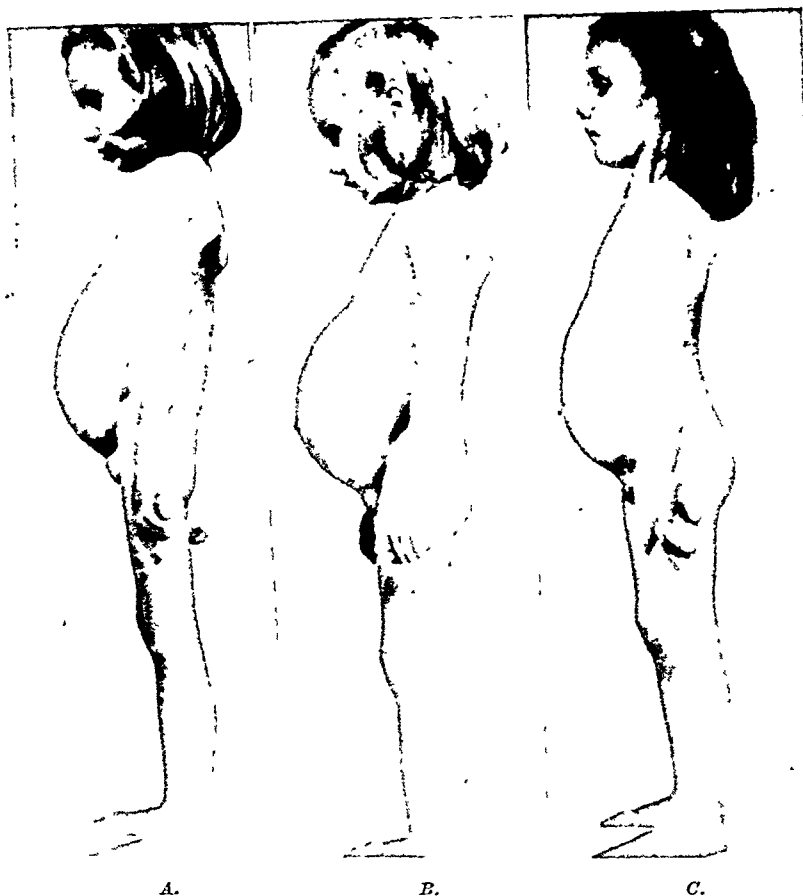


Fig. 5.—B. H. A, At 3½ years. B, Six weeks later. C, At 3 years, 11 months. During the early stages of improvement, the abdomen becomes larger; later, the abdominal enlargement becomes moderate and there is a tendency to obesity.

There is evidence that several phenomena consistently found during the critical period but not known to be due to the deficiency of a specific substance are transitory and hence are probably not essential parts of the basic process. Among these is steatorrhea, which will be discussed more fully, since it has been long considered essential to the diagnosis of celiac disease. In obtaining the data to be presented, a standard procedure was followed. These data consist of a series of analyses of the feces for fat, and in all instances the feces were collected while the patient was receiving a normal diet for his age, which included whole milk, either pasteurized or evaporated. The patient was placed on the diet twenty-four to forty-eight hours before the beginning of the stool collection, and

this diet was continued throughout the three-day period of the collection. The total material was placed in a single container, thoroughly mixed, and aliquots were then taken for various analyses. The results are reported in terms of per cent of dried weight as total fat and also as the mean weight of fat excreted per day.

The evidence that steatorrhea is not part of the basic process may be summarized as follows:

The first observation was that some patients who present the complete physical appearance of celiac disease and who excrete large, pale, foul stools do not in fact have an excess of fat in the feces either before or after the appearance of diarrhea on a normal diet (Table I). It was this observation that led me, some years ago, to postulate the existence of starch intolerance as a disease entity distinct from celiac disease, an hypothesis which subsequent experience has led me to retract.

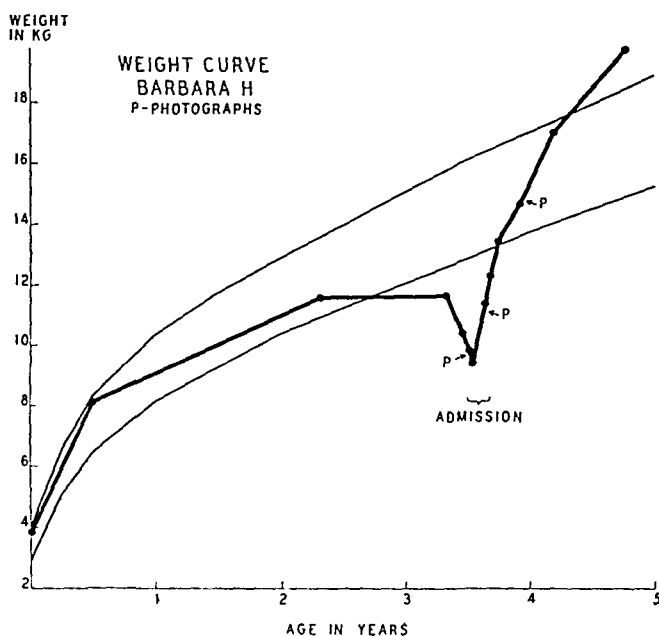


Fig. 6.—B. H. Weight curve showing long prodromal period preceding the critical period at 3 years.

Patients who showed marked steatorrhea on the first examination made after admission to the hospital usually no longer showed steatorrhea after clinical improvement, the change taking place within a period of less than a year (Table II).

Patients who, on admission, were considered so ill that trial with normal diet was hazardous but who were placed on a normal diet after a few weeks of therapy were sometimes found to have no excess of fecal fat. In nine patients a preliminary microscopic examination of the feces showed an excess of fat even though the patient was receiving a limited fat intake and a protein milk formula,

but examination a few weeks later while the patient was on a normal diet including whole milk revealed no excess of fat by either microscopic or chemical examination. I present the photographs and weight curve of one such patient (Figs. 9 and 10) to demonstrate the severity of the disease and the similarity to the cases with steatorrhea previously presented.

The time required for the disappearance of steatorrhea after the initiation of therapy has not been determined with exactness, chiefly because the possibility that it might be brief did not occur for some time. An estimate may be made by arranging the data obtained from the more severely ill patients with respect to the interval between admission to the hospital and the determination of the relative amount of fat in the feces (Table III). From these data it would appear that steatorrhea is usually overcome within one month of the beginning of therapy, and in the present series it has been found after two months in only one case. It is not uncommon, however, to find a mild increase in fecal fat in terms of grams of fat excreted per day when the total daily

TABLE I. FECAL FAT IN CELIAC DISEASES BEFORE AND AFTER "BREAK" ON NORMAL DIET IN PATIENTS WITHOUT STEATORRHEA

PATIENT	AGE (MO.)	BEFORE				AFTER			
		STOOL (GM./DAY WET WT.)	WATER (%)	FAT (%) DRY WT.)	FAT (GM./ DAY)	STOOL (GM./DAY WET WT.)	WATER (%)	FAT (%) DRY WT.)	FAT (GM./ DAY)
C. C.	14	—	84.1	15	—	75	84.4	14	2.1
M. S.	17	38	71.2	12	1.3	—	73.7	7	—
M. M.	21	49	70.4	27	3.9	88	81.4	25	4.0
J. F.	26	32	74.7	9	0.8	40	79.0	12	1.0
Controls	12 to 24	34.6	77.5	13.7	0.95				
(Mean and S.D.)		±14.7	±4.0	±5.6	±0.33				

TABLE II. STOOL FAT AND CELIAC DISEASE; EFFECT OF TREATMENT ON STEATORRHEA

PATIENT	AGE	BEFORE				AFTER		
		STOOL (GM./DAY WET WT.)	FAT (% DRY WT.)	FAT (GM./ DAY)		STOOL (GM./DAY WET WT.)	FAT (% DRY WT.)	FAT (GM./ DAY)
E. J.	7 months	69	43	6.7	8 months	56	17	2.0
R. F.	11 months	43	48	5.3	21 months	44	12	1.0
S. E.	16 months	80	34	3.8	24 months	61	11	1.1
R. T.	22 months	25	57	1.7	2½ years	76	21	3.7
L. I.	3½ years	62	44	6.0	4 years	93	26	2.6
M. G.	4 years	150	24	7.9	4½ years	128	17	2.8
Controls	6 to 12 months	26 ±10.5	18 ±4.9	1.0 ±0.4				
(Mean and S.D.)	1 to 2 years	35 ±14.7	14 ±5.6	1.0 ±0.3				
	2 to 6 years	26 ±15.5	15 ±2.7	1.0 ±0.5				

TABLE III. RELATION BETWEEN DURATION OF THERAPY AND EXCESS FECAL FAT IN PATIENTS WITH THE CLASSICAL CLINICAL PICTURE OF SEVERE CELIAC DISEASE: NUMBER OF CASES

FECAL FAT (% DRIED WT.)	DURATION OF THERAPY IN WEEKS								
	1	2	3	4	5	6	7	8	>8
Over 30%	10	2	2	4	0	0	1	0	1
Under 30%	5	5	3	0	1	3	0	0	12

excretion of feces is excessive. In these circumstances, there is no selective excess in fat excretion, and the absolute increase may be interpreted as the result of mechanical difficulty or of the increase in fecal fat derived from bacteria. The daily excretion rarely exceeds 3 Gm. of fat-per day.

Observations on the lipase concentration in the duodenal juice confirm previous reports that this is normal, and that the difficulty in fat utilization cannot be satisfactorily attributed to failure to split fat (Table IV). By elimination, this leads to the assumption that the difficulty must lie either in a later process necessary for absorption of fat, such as the phosphorylation of fatty acids, or in the absorptive process itself, both of which may be assumed to be enzymatic in nature.

TABLE IV. LIPASE IN THE DUODENAL JUICE OF PATIENTS WITH CELIAC DISEASE AND STEATORRHEA

AGE	CONDITION	NO.	LIPASE, UNITS 100/C.C.	
			MEAN	S.D.
6-12 months	Steatorrhea	3	26.1	9.6
	Controls	11	26.1	21.2
1-2 years	Steatorrhea	11	25.1	17.8
	Controls	9	18.8	11.1
2-5 years	Steatorrhea	4	40.7	16.7
	Controls	13	19.6	12.8

The observations just presented provide indirect confirmation of May's earlier one<sup>6</sup> that intensive therapy with vitamin B complex and liver concentrates restores the normal vitamin A absorption curve within a short period, since steatorrhea can be correlated with poor absorption of vitamin A. We are led to the thought that both steatorrhea and poor absorption of vitamin A may be the result of a deficiency of some dietary factor required by the intestine for the normal absorption of fat. The work of May, McCreary, and Blackfan<sup>6</sup> indicates that this substance is to be sought among the members of the vitamin B complex, and the question should be explored further. The records of the patients of the present series provide evidence that therapy with vitamin B complex does not restore complete tolerance to a normal diet nor does it terminate all of the phenomena of the critical period.

It is not possible to discuss here the other phenomena of the critical period, which, in most cases, respond promptly to therapy. Some of them are enumerated as follows: muscle atrophy and consequent flat buttocks; relaxation of ligaments; irritability and apathy; anorexia; a flat glucose tolerance curve; osteoporosis; low concentrations in the serum of cholesterol, lipids, carotene, and positive inorganic ions. These cannot be considered as necessary attributes of the underlying constitutional difficulty.

If the critical period is the expression of a multiple deficiency state which develops under adverse circumstances in patients who have an underlying constitutional defect, it is reasonable to believe that some children with the same basic defect escape the complete expression of the disease. This concept receives

support from the common experience that the clinical picture varies greatly in degree in different cases. Confirmatory evidence is the observation that the incidence of the complete and easily recognized phase of the disease has increased many fold during the war in various cities in Europe, including some where food was relatively abundant though limited in variety, such as London, Copenhagen, and Stockholm. The chief difficulty in establishing the hypothesis that celiac disease is based on an underlying constitutional defect is the dearth of objective criteria of this defect. To return to the analogy with diabetes, it is as though we were unable to make the diagnosis of diabetes in the absence of coma.

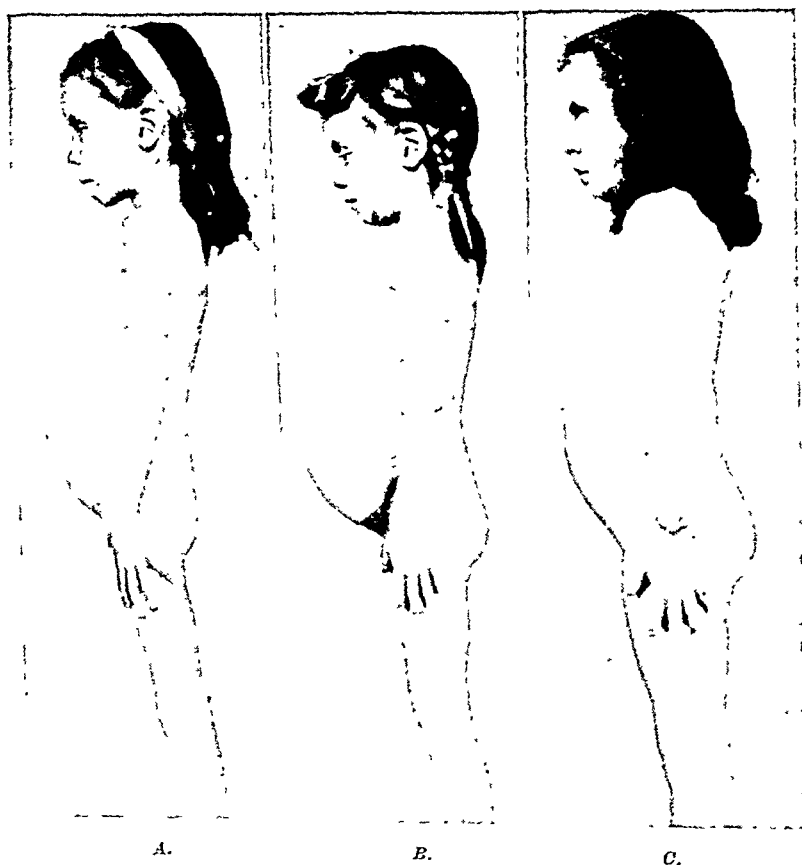


Fig. 7.—P. M. A, At 6 years, 10 months. B, Twenty-three days later. C, At 7 years, 5 months. The changes are similar to those in the previous cases, although the critical period has occurred at a later age. Improvement in morale is expressed in the hair-do.

The expressions of the basic constitutional disease may be assumed to be present in patients during the critical phase and to persist after the transitory phenomena have responded to dietary therapy. They should also be demonstrable in milder cases in which the complete deficiency state has not been reached. One or more characteristics of the basic disease should be of such nature as to induce diarrhea and a multiple deficiency state. In the course of



these studies, a group of clinical and laboratory findings relating to inadequate digestion of starch has been consistently found in severely ill patients, in those who are convalescent from the critical state, and also in milder cases which have been previously described under the name of starch intolerance. If the presence of steatorrhea is not required for the diagnosis of celiac disease, there are no features which distinguish the patients with starch intolerance from those in the prodromal or recovery phases of celiac disease with steatorrhea. In addition to the factors relating to starch digestion, there are several other phenomena which are so commonly present as to deserve further investigation as to their place in the disease. The characteristics which are consistently present include the following:

1. Pancreatic amylase is absent from the duodenal juice or present in small quantity only. There is clinical intolerance to starch in the diet, clinical response to elimination of starch from the diet, and an excess of starch in the feces when starch is fed.

2. The requirement of dietary protein is greater than normal, as indicated by clinical response to elevated dietary protein and the frequent occurrence of hypoproteinemia in patients who have received dietary protein at levels usually found adequate.

3. There are intermittent attacks of diarrhea, usually beginning in the first year and most severe during the second year, with gradual decrease in severity and frequency as school age is approached.

4. The attacks of diarrhea are usually initiated by an upper respiratory infection and may be controlled either by restriction of the diet or by the administration of sulfadiazine.

5. If the milder cases without steatorrhea be included, there is a high familial incidence of the disease. Commonly, one sibling has celiac disease with steatorrhea and the other is less severely ill with starch intolerance. Several examples of a familial incidence of severe cardiac disease with steatorrhea have been encountered in the past two years.

At the present time the objective findings which are of most value in the recognition of uncomplicated celiac disease are those relating to starch indigestion, specifically the deficiency of amylase in the duodenal juice and the excess of starch in the feces when starch is fed. The importance of these two determinations warrants a brief discussion of the technical difficulties encountered in obtaining and interpreting the data. In regard to the assay of amylase in the duodenal juice, three such obstacles should be considered. The first of these is the frequent admixture of gastric juice with the duodenal contents, resulting in varying degrees of dilution of the pancreatic juice. The use of a double-lumen Einhorn tube with separate openings for the drainage of gastric and duodenal juice has so far not been successfully applied to small infants. In the material obtained with a single tube from the duodenum it may be assumed that the various pancreatic enzymes are equally diluted. Since the method for determining trypsin is more reliable than that for lipase, and since trypsin has been found in high concentration in nearly all cases except

those with fibrocystic disease of the pancreas and those in extreme marasmus, this value has been taken as the figure of reference, and the ratio of amylase to the concentration of trypsin expressed in viscosimetric units has been used in evaluating the degree of amylase deficiency. Comparison of the absolute concentration of amylase in the duodenal juice of patients with celiac disease and controls of like age shows a difference which is statistically significant but less impressive than the difference in the ratio.

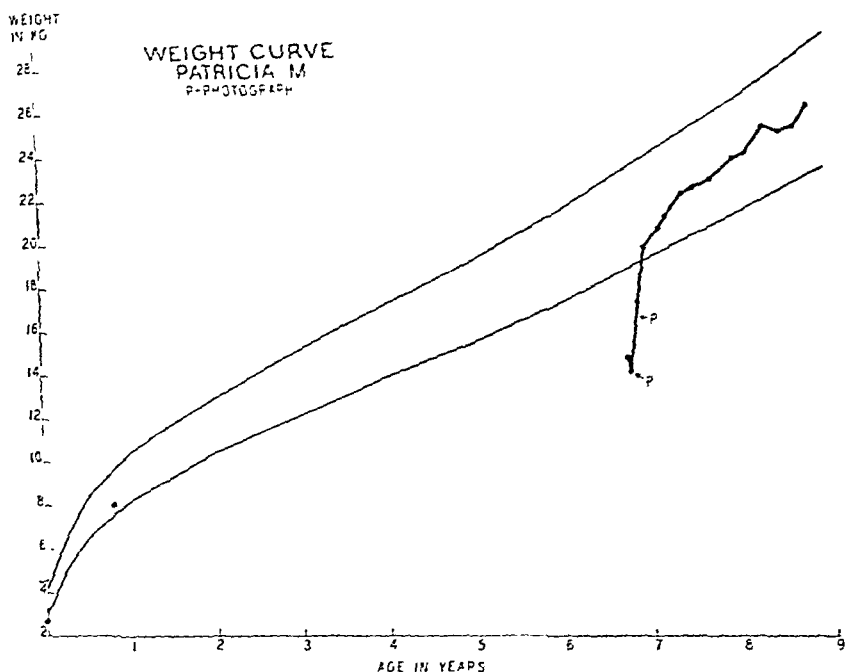


Fig. 8.—P. M. Weight curve.

The second difficulty to be considered is the frequent occurrence of gastric hypoacidity in patients with celiac disease either with or without steatorrhea. When the gastric juice contains little or no free acid it frequently contains amylase which has its source in swallowed saliva. When an admixture of this gastric juice with pancreatic juice is recovered from the duodenum, there may still be some salivary amylase in it, giving an erroneous impression that amylase is being secreted by the pancreas. Thus diluted, the concentration is never high, usually giving a ratio of amylase to trypsin of less than 20 per cent. It is possible to obtain results of this order in the complete absence of pancreatic amylase.

The third technical difficulty results from the fact that amylase is normally absent from the duodenal juice in the neonatal period, and that the normal ratio of amylase to trypsin in the second half of the first year is of the order of 50 per cent, while after one year of age it ranges between 50 per cent and 150 per cent. The determination of amylase concentration cannot therefore be used to sub-

stantiate the diagnosis in infants under 6 months, even though clinical symptoms may appear before this age. As a working rule the value of this ratio which marks the dividing line between normal and abnormal is taken as 20 per cent for patients between 6 and 12 months of age and 40 per cent for those who are older (Table V).

TABLE V. RATIO OF AMYLASE TO TRYPSIN IN THE DUODENAL JUICE IN CELIAC DISEASE  
EXPRESSED IN VISCOSIMETRIC UNITS

AMYLASE/ TRYPSIN ×100	AGE 6-12 MONTHS			AGE 1-10 YEARS		
	CELIAC DISEASE		CONTROLS	CELIAC DISEASE		CONTROLS
	STEATOR- RHEA	NO STEAT- ORRHEA		STEATOR- RHEA	NO STEAT- ORRHEA	
0-20	6	10	3	17	26	5
20-40	0	0	6	7	10	3
40-60	0	0	1	0	1	6
60-80	0	0	3	1	1	4
80-100	0	0	0	0	2	4
100+	0	0	1	1	0	13
Total	6	10	14	26	40	35

The frequency of gastric hypoacidity in celiac disease and the lack of correlation between gastric acidity and the presence of steatorrhea are shown graphically in Fig. 11.

The influence of the gastric acid on the value of amylase was first suspected because of several instances in which an initial determination, made when the patient was marasmic, showed a moderate concentration of amylase, while a subsequent determination, made after marked clinical improvement, gave a value of zero. It was subsequently found that the reverse was sometimes true of the free and total acid of the gastric juice (Table VI). This hypothesis was confirmed in a somewhat complicated experiment in which pure salivary secretion, gastric juice, and duodenal juice were obtained from a patient with celiac disease who lacked free gastric acid and from a control patient with a central nervous system disorder who had never suffered digestive difficulties. The values for amylase from these three sources and from both patients were compared and it was then shown that the control gastric juice had the power to destroy amylase, that this power was lost after neutralization, and that the neutral gastric juice

TABLE VI. CHANGE IN GASTRIC JUICE WITH CLINICAL IMPROVEMENT IN  
PATIENTS WITH CELIAC DISEASE

PATIENT	AGE	VOLUME (C.C.)	FREE ACID UNITS	TOTAL ACID UNITS
D. C.	1½ years	32	19	59
	3½ years	54	42	87
J. M.	1½ years	3	0	29
	1½ years	32	20	58
C. M.	9 months	11	5	15
	10 months	51	12	35
J. F.	7 months	10	0	25
	9 months	20	0	33

TABLE VII. COMPARISON OF AMYLASE FROM VARIOUS SOURCES IN A SEVERE CASE OF CELIAC DISEASE AND A CONTROL CASE

SOURCE	M. M., AGE 18 MO. CELIAC DISEASE (AMYLASE UNITS/C.C.)	J. M., AGE 24 MO. CONTROL (AMYLASE UNITS/C.C.)
Saliva	625	745
Gastric juice	60	0
Duodenal juice	32	152
Blood	0	Mean of controls 0.15

TABLE VIII. EFFECT OF GASTRIC JUICE ON DUODENAL AMYLASE

SOURCE	DUODENAL JUICE, AMYLASE UNITS/C.C.	
	M. M., CELIAC DISEASE	J. M., CONTROL
Duodenal juice	32	152
Incubated 10 minutes with M. M.'s gastric juice	38	158
Same with J. M.'s gastric juice	0	0
Same with J. M.'s neutralized gastric juice	35	127

of the celiac patient lacked the power to destroy this enzyme. The data of this experiment are presented in Tables VII and VIII.

The examination of the feces for starch also presents some difficulties. The method which has been found most useful is the traditional one of microscopic examination of a smear of a fresh sample stained with Lugol's solution. Specimens which have remained at body temperature or at room temperature for twenty-four hours or more often fail to show starch, even when this was present in the fresh specimen, presumably because of digestion by bacteria. Consequently, negative findings in a sample obtained after a day or two of constipation should be disregarded and all samples should be examined before they are many hours old. A distinction should be made between iodine-staining material within vegetable or banana cells and the finer extracellular granules which are not protected by a cell membrane. The intracellular granules are normally present in the feces of infants and young children. It is reasonable to explain the survival of undigested starch on the basis of protection by the cell membrane from enzymatic and bacterial action. Extracellular granules are not found in any considerable quantity in the feces of normal infants over 6 months of age and are abundant in the feces of children with celiac disease or starch intolerance with or without steatorrhea who have been fed cereal starch or potato. Elimination of these foods from the diet results in the disappearance of extracellular starch from the feces of these patients. It appears, therefore, that in the absence of pancreatic amylase some of the ingested starch which is unprotected by a cell membrane can escape digestion throughout passage of the intestinal tract. The presence of this starch may be presumed to contribute directly or indirectly to the production of other abnormalities of the feces which are characteristic of the disease, such as the foamy fermented appearance, acid reaction, and the alterations of the fecal flora in favor of gram-positive cocci, which are known to occur. As an illustration it may be mentioned that yeast cells having the morphology of

Monilia and staining with iodine are frequently seen in samples of feces which contain much extracellular starch and are rarely encountered otherwise; their presence is thus of some diagnostic value. The microscopic examination of the feces for starch is therefore a brief, simple, and, if due precautions are observed, a reliable diagnostic aid.



Fig. 9.—J. B. *A*, At 18 months. *B*, At 20 months. On admission, the feces contained only 22.5 per cent fat on a dried basis. In spite of absence of steatorrhea, the physical appearance and weight curves are similar to those of the previous patients

Whether the failure to digest starch and the consequent abnormalities of the intestinal contents and of the feces can in some way lead to deficiency of the vitamin B complex remains to be investigated. Past observations on the intestinal flora in celiac disease have contributed the information that enteric pathogens are usually absent but that the flora are altered. With the newer concepts of the role of intestinal bacteria in the formation and destruction of vitamins and with the evidence here presented that undigested starch is present in the intestine and may be assumed to alter the characteristics of the intestinal contents as a culture medium, the question of the role of intestinal bacteria in celiac disease should be reopened.

The evidence relating to starch indigestion in celiac disease has been presented in some detail because it is at present well supported by laboratory and clinical evidence; it also has immediate practical application in the diagnosis and treatment of the disease. Close observation of patients has yielded fragments of evidence that the basic disease has more attributes than lack of amylase secretion and consequent failure to hydrolyze starch. There is an almost universal clinical response to a high protein diet and a tendency to hypoproteinemia on a diet which contains protein at levels which are adequate for normal infants.

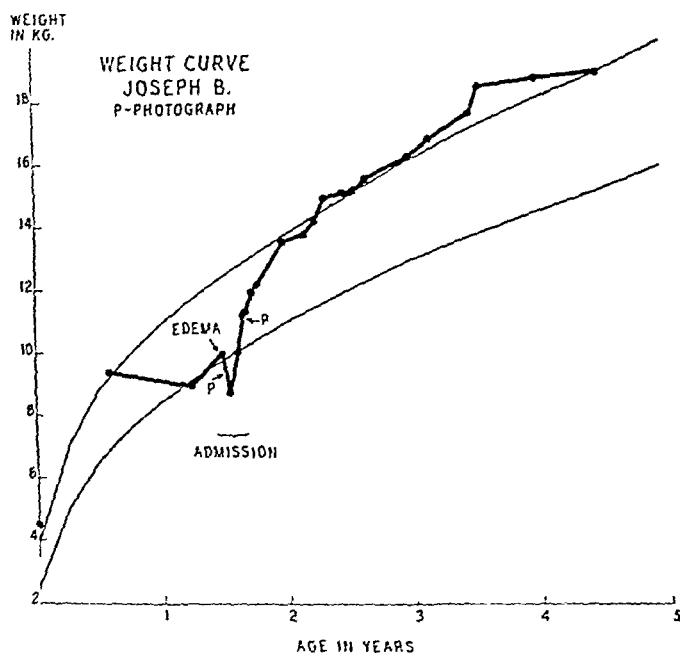


Fig. 10.—J. B. Weight curve.

This cannot be explained on the basis of a loss of nitrogen in the feces, for according to our data this is usually within normal range. It has recently been reported that amino acid absorption is normal in celiac disease.<sup>7</sup> There is therefore indirect evidence of a defect in protein metabolism in most, if not all cases; it is not yet clear whether this is a necessary part of the basic constitutional defect.

There are a number of other abnormalities which are commonly but not universally present, the relationship of which to the disease is not yet clear. Some of these are enumerated as follows:

1. Gastric hypoacidity and sometimes hypochylia. This is as common in mild as in severe cases. In many instances it has been reversible.
2. A variety of types of anemia, significantly more common in cases with gastric hypoacidity. This is probably a secondary phenomenon.

3. Abnormal gastrointestinal motility with evidence of a "deficiency pattern," demonstrable by serial roentgenograms following a barium meal.

4. Osteoporosis and delay in bone maturation in the presence of normal levels of serum calcium and phosphorus and in the absence of rickets.

### GASTRIC ACIDITY IN CELIAC DISEASE

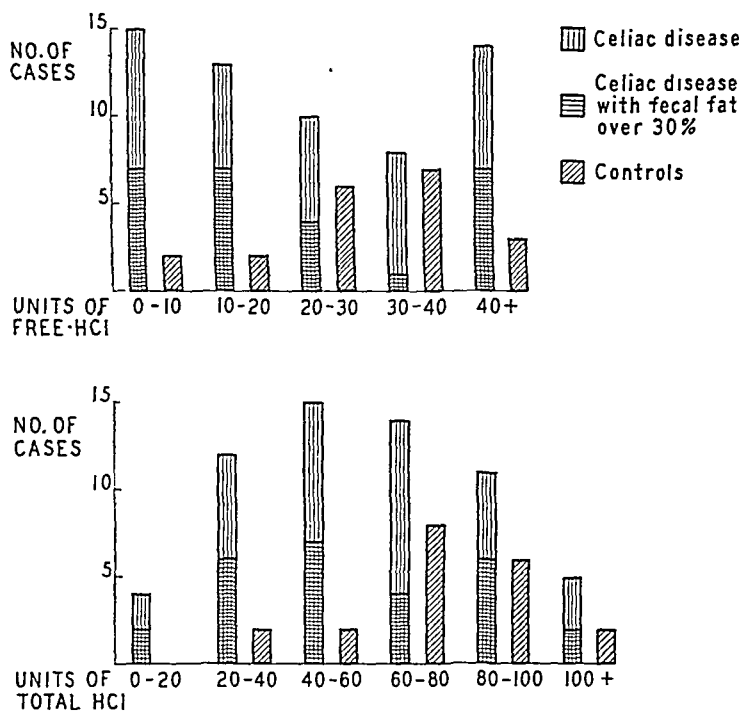


Fig. 11.

Because of the recent suggestion that celiac disease is the result of gastrointestinal allergy<sup>s</sup> our experience in this regard should be mentioned. Among eighty-one records of the present series, fourteen have been found with a history of allergy as defined by the presence of asthma, hay fever, severe eczema or proved gastrointestinal allergy. Of these, nine were considered to have major allergy. Two had normal levels of amylase and probably do not have celiac disease on a basis of starch intolerance. They may be said to present the celiac syndrome on the basis of gastrointestinal allergy. In the remaining sixty-seven charts of the present series, evidence of allergy in the patient has been absent or unconvincing. This incidence is not significantly greater than has sometimes been estimated for the general populace.

The evidence which has been presented that the steatorrhea of celiac disease is a transitory and inconstant phenomenon while difficulty in starch digestion is a constant finding which persists at least during the first five years of life, gives us a new background for the evaluation of the various regimes popular in the past. The diet which was devised about five years ago for

patients with starch intolerance and has proved successful in these patients and in those who have recovered from the acute steatorrheal phase of celiac disease does not differ greatly from some of the traditional ones arrived at empirically. Its characteristics are as follows:

1. It is high in protein, supplied as meat, cheese, egg, fish, and milk. Protein milk is given the younger patients and those recently recovered from the critical phase, while the majority of the others do well on whole milk.

2. Limited amounts of fat are given to young infants and to those recently recovered from a crisis. Moderate amounts are supplied to patients in good condition in the form of whole milk, butter and bacon. An excess of fat is avoided and fried foods are prohibited.

3. Carbohydrate is given in abundance and is supplied as simple sugars or disaccharides. Glucose, bananas, and fruit juices are the usual sources in the case of more severely ill patients. Cooked vegetables and raw apples and pears are soon added. Cane sugar is tolerated well within a few weeks of recovery from the acute phase. Care is taken to distribute the sugar throughout the day so that an excessive amount at any one meal is avoided. Cereal starches, bread, and potatoes are withheld for a year or more after recovery from the severe symptoms and are then given cautiously and in limited amounts.

4. Vitamin supplements include ascorbic acid, a fish liver oil concentrate, and vitamin B complex, all given orally. The preparation of vitamin B complex is selected not only for its thiamin content but on the basis of whether it contains the estimated daily requirements of pyridoxin, riboflavin, nicotinamide, calcium pantothenate, and folic acid. The daily dose has been designed to provide at least double the estimated daily adult requirement of these substances. No parenteral vitamin therapy is given, except in certain cases of severe anemia, in which liver extract is injected intramuscularly three times a week for a period of a few weeks.

A diet based upon these principles can be made varied and general and is usually well taken. It has been successfully applied to well over 100 patients. A patient with celiac disease when on this regime no longer has the characteristic stools, although the bulk may sometimes decrease only gradually. There may be a few loose stools on the first day or two of an acute respiratory infection, but this mild diarrhea responds either to a few days of restricted diet or to the administration of sulfonamides without alteration of the diet. The premature addition of bread, crackers, or other starch will result in resumption of loose pale stools after an interval of a day to several weeks or with the next upper respiratory infection. The relationship of starch ingestion to the abnormal stools is clearly shown in some of the cases: one boy regularly had loose stools on Mondays, following the Sunday visit to his grandmother. Another example is the patient R. T., reported here, who failed to respond to vitamin therapy while on a diet high in starch but responded promptly when dietary therapy was also given.



## SUMMARY

The classical picture of celiac disease is believed to result from a deficiency of multiple nutritional factors complicating and resulting from a basic constitutional disease. The steatorrhea of celiac disease is transitory, and with intensive vitamin and dietary therapy it disappears within two months; it is viewed as a complication of celiac disease due to a specific deficiency and comparable in this regard to rickets or scurvy. A consistent and objectively demonstrable characteristic of the basic disease is a deficiency of pancreatic amylase, associated with an excess of starch in the feces when starch is fed and clinical intolerance to dietary starch. In uncomplicated cases the presenting symptom is the occurrence of repeated bouts of diarrhea with large, foul, pale, foamy stools and an enlarged abdomen. These bouts are usually initiated by an upper respiratory infection. The symptoms respond to a diet high in protein, low in starch, and abundant in vitamins. The classical picture of celiac disease with steatorrhea is the result of a multiple deficiency state superimposed on the basic disease under adverse circumstances. An attempt is made to evaluate other phenomena of the disease with respect to whether they are part of the primary defect or a result of secondary nutritional deficiency. There is suggestive evidence that the difficulty in protein metabolism, shown by the high requirement for dietary protein and a tendency to hypoproteinemia on a normal diet, may be an expression of the basic disease.

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# AN EVALUATION OF BENADRYL, PYRIBENZAMINE, AND OTHER SO-CALLED ANTIHISTAMINIC DRUGS IN THE TREATMENT OF ALLERGY

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THERE is more than one school of thought with respect to the genesis of hypersensitive phenomena. The toxic or anaphylatoxin theory was based on the assumption that an antigen to which an animal is sensitized, when re-injected, is split by proteolytic ferments into toxic degradation products which produce the now well-known symptoms characteristic of the hypersensitive state. This early concept was later modified by a substantial amount of evidence favoring the hypothesis that histamine is liberated from the tissues during the antigen-antibody inter-reaction, and that the symptoms of anaphylaxis and allergy are, therefore, directly attributable to the action of the released histamine. In recent years, the advocacy of this hypothesis by several staunch proponents has awakened a renewed interest in the search for chemical or biologic substances capable of abolishing or diminishing some or all of the effects of the released histamine.<sup>1-6</sup>

Hill and Martin,<sup>7</sup> in 1932, critically reviewed 165 substances or methods that might serve to inhibit anaphylaxis nonspecifically, and they came to the conclusion that none were ideal for the purpose. In the succeeding years, considerable additional experimentation was done, but the interpretation of results in most instances is open to question according to Feinberg<sup>8</sup> who reviewed much of it in 1944.

One of the first of this series was the enzyme, histaminase, which destroys histamine *in vitro*.<sup>9</sup> It was recommended for oral and parenteral use. Although it was received with great *éclat* and was enthusiastically advocated for the relief of all forms of allergy (under the trade name of Torantil), it soon found its resting place as another of the many ineffectual remedies.<sup>10, 11</sup>

Fell and his co-workers<sup>12, 13</sup> offered still another approach to the problem by developing a substance which became known as hapamine. It is a histamine-hapten combination with despeciated, normal, horse serum globulin. The underlying concept was that injections of this substance would produce antibodies against histamine and thus fortify the individual against the allergic symptoms induced by liberated histamine. The procedure proved unsound not only because it did not produce any immunity but because it induced sensitivity to the new hapten antigen in a number of instances.

We are now in the throes of experimenting with a new series of so-called antihistaminic drugs. The two drugs most widely advocated are Benadryl, a Parke, Davis product which was studied by Loew and associates,<sup>14-16</sup> and Wells and associates,<sup>17, 18</sup> and Pyribenzamine, a Ciba product reported upon by

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Mayer.<sup>19, 20</sup> News of the experimental and clinical investigations was catapulted upon the public and medical profession alike through the medium of the lay press, including the *Saturday Evening Post*, *Life*, and newspapers throughout the country.

These new synthetic chemical formulas are complex structures involving the benzene rings. Benadryl is  $\beta$ -dimethyl-aminoethyl benzhydryl ether hydrochloride. Pyribenzamine is N-pyridil-N-benzyl-N-dimethylethylenediamine monohydrochloride.

From a historic viewpoint, it may be of interest to know that these drugs were preceded by numerous compounds chiefly of French lineage, e.g., 929 F and 1571 F,<sup>21-23</sup> and 2339 R. P., known as Antergan,<sup>24</sup> all having antihistaminic and antianaphylactic properties. Newer French preparations, such as compound 2786 R. P., known as neoantergan,<sup>25</sup> are less toxic and are attended with considerable clinical success according to the French literature. The story of the evolution of these drugs and an evaluation of them have been given in detail by Feinberg,<sup>11, 40</sup> Code,<sup>26</sup> and Mayer.<sup>20</sup>

Anthallan, another coal tar derivative, was introduced to the profession through a widespread presentation of its merits in the lay press, and through a clinical analysis by Ghiselin.<sup>27</sup> The *Journal of the American Medical Association*, commenting editorially on the Ghiselin study,<sup>28</sup> stated: "Notably lacking in this report are parallel studies on control patients, or, in fact, any controls whatsoever." Final judgment on the value of anthallan must be deferred.

#### PHARMACOLOGIC ACTION

According to some investigators,<sup>14-24, 29</sup> pharmacologic studies suggest that these antihistaminic drugs have three important actions. They alleviate (1) smooth muscle spasm, (2) bronchial constriction caused by histamine or anaphylactic shock, and (3) vasodepressor effects of histamine.

From the fact that they counteract the spasmogenic effects of barium chloride and acetylcholine, it has been concluded that these drugs must also possess a musculotropic, antispasmodic action and neurotropic effects (atropine-like). Epstein<sup>30</sup> believes that these drugs must possess additional pharmacologic qualities as evidenced by their sedative effect.

During prolonged drug administration in dogs, no progressive changes were noted in the blood counts, hemoglobin, and nonprotein nitrogen values. The differential blood counts also remained at levels close to those of the pretreatment period. Histologic studies showed no evidence of acute or chronic degenerative processes in any of the organs. The choroid plexus, however, appeared somewhat more congested than usual.<sup>31</sup>

Reinstein and McGavack<sup>32</sup> found that unlike the epinephrine type compounds, benadryl does not produce an increase in pulse rate and blood pressure in man, but, on the contrary, lowers blood pressure and causes drowsiness. Benadryl given by mouth has no apparent effect on glucose tolerance. When given intravenously it appears to increase sugar tolerance, a phenomenon which may be mediated through the liver. Friedlaender and Feinberg<sup>33</sup> also noted a fall in blood pressure.

McElin and Horton<sup>34</sup> showed that the action of benadryl on gastric secretion in man is somewhat inconsistent; only in some instances was the ability to block the gastric response to histamine demonstrated.

The effects of these drugs in reducing urticaria, drying up the secretions of hay fever, and producing dryness of the mouth may be due to the blocking of the secretagogue action of histamine. These activities may also be due to antihistaminic effects on blood vessels. The dryness of the mouth may be interpreted also as an atropine-like effect. Speculation concerning the drowsiness, disorientation, jitteriness, and many other profound influences on the upper brain centers would lead us far afield and without profit at this stage of our knowledge.

Friedlaender and Feinberg<sup>33</sup> did some valuable studies on experimental whealing in the human subject in relation to benadryl and pyribenzamine. They found that oral administration of either caused only a slight impairment in the development of experimentally produced histamine wheals. The direct local application to skin sites results for a limited time in a reduction of any histamine reaction subsequently produced in that site. This effect may also be obtained by combining the antagonist directly with the histamine solution. An almost identical action was obtained on ragweed-tested wheals, wheals produced by codeine, morphine, atropine, pilocarpine, physostigmine, and bee venom on skin sites previously treated with the antagonist. Pyribenzamine appeared to have greater activity than benadryl.

Arbesman and associates<sup>35</sup> found that pyribenzamine given orally reduced the size of histamine wheals in eighteen of twenty-eight subjects and reduced skin reactivity in fourteen of twenty-four allergic patients. Such oral administration also reduced the reactivity of skin sites passively sensitized with a serum containing cottonseed reagins.

*Passage Through Breast Milk and Placenta.*—A patient seen with Dr. Harold J. Eisenberg of New Rochelle is of interest because of the suggestive demonstration of the passage of these drugs through the breast milk.<sup>36</sup>

A nursing mother was given 50 mg. of benadryl every three hours to relieve a contact dermatitis. After the third dose it was observed that the breast-fed infant, 5 weeks old and normal in every respect, became quite lethargic. However, therapy was not discontinued until three days later, when the lethargy and constipation of the infant became very marked. The infant was then taken off the breast and placed on an evaporated milk formula. Twenty-four hours later, the infant's symptoms all disappeared.

I have little doubt that these drugs will show an equal or greater readiness to pass through the placenta because of the great permeability of the placental barrier.<sup>37</sup>

#### MODE OF ACTION OF BENADRYL AND PYRIBENZAMINE

Although these drugs are said to be antihistaminic, proof for such a concept is by indirection. As Code<sup>36</sup> has pointed out, because benadryl relieves symptoms is not conclusive proof that these symptoms are due to histamine. The contention of Loew and Kaiser<sup>34</sup> is: "In view of the fact that these synthetic benzhydryl ethers are effective in alleviating both histamine shock

and anaphylactic shock, the data constitute additional *indirect* evidence that the chief symptoms of anaphylaxis are referable to histamine."

Wells and his associates<sup>18</sup> express the belief that the chemical structure of benadryl ( $\beta$ -dimethyl-amino-ethyl-benzhydryl ether) suggests that direct chemical interaction with histamine is improbable. They imply that if benadryl or pyribenzamine combines with the receptive substance, it prevents the histamine from combining at the same site. This mode of drug antagonism is demonstrated also in the competition between para-aminobenzoic acid and sulfonamides, atropine and acetylcholine, and ergotoxine and epinephrine.

Further pharmacologic studies with benadryl by Loew and associates<sup>18</sup> lead them to conclude: (1) histamine is not inactivated because of chemical union or neutralization, for if it were so, one would expect greater antagonism of the gastric secretagogue action of histamine; (2) benadryl does not neutralize histamine stoichiometrically, because a four-times weaker dilution of benadryl than that of histamine prevented the spasmogenic action of the latter; (3) because benadryl prevented the spasmogenic action of barium and acetylcholine on intestinal smooth muscle, it is unlikely that benadryl chemically neutralizes such dissimilar substances as histamine, barium, and acetylcholine; (4) the antagonism toward these substances suggests the more probable explanation that the drug alters the permeability of smooth muscle or combines with some portion of the effector cell so as to prevent histamine or other spasmogenic agents from producing a normal response.

Halpern<sup>24</sup> is of the opinion that these drugs so modify the reaction of the allergically affected organ that histamine is incapable of exercising its customary effect. They do not prevent the liberation of histamine or increase its destruction. This conclusion is supported by the observation of Wells and associates,<sup>17</sup> who show that benadryl does not materially interfere with the release of histamine during anaphylactic shock in dogs.

In view of this and other evidence<sup>20</sup> that these drugs do not inactivate histamine because of chemical union or neutralization, it would seem more logical at this point to attribute to these drugs the capacity to counteract the musculotropic effect of antigen-antibody or histamine reactions, rather than to describe them as antihistaminic or competitive drugs.

A study by Curry<sup>30</sup> has just been published, which casts further doubt on the assumption that these drugs are specifically antihistaminic, or that they differ too markedly from other antispasmodic drugs in their action. He investigated the effects of bronchoconstriction resulting from the intravenous injection of histamine in human beings by an ingenious method. He found that benadryl, pyribenzamine, atropine sulfate, aminophylline, epinephrine, and ephedrine all gave protection against histamine bronchoconstriction.

Despite the finding that benadryl and pyribenzamine do interfere with anaphylaxis and histamine shock in guinea pigs and dogs if given in large amounts, they have been signally ineffectual in relieving asthma. The conclusion which should be drawn from the anaphylaxis studies of Wells, Morris, and Dragstedt,<sup>17</sup> Loew and Kaiser,<sup>14</sup> and Mayer,<sup>20</sup> is that these drugs alleviate

anaphylactic shock somewhat when given in large doses, but do not afford real and unquestioned protection of a constant and high degree.

Mayer<sup>20</sup> asserts: "The challenge of these substances is that they should enable us to test, extend, or restrict the histamine theory of allergy."

From their mode of action it is obvious that these drugs can act only as palliative agents and do not eliminate the basic mechanism responsible for allergic symptomatology.

#### CLINICAL EVALUATION OF THE SO-CALLED ANTIHISTAMINIC DRUGS

It is well nigh impossible to evaluate the efficacy of any drug in allergic diseases with any degree of accuracy, because: (1) the criteria for measuring the benefits are not uniform and are for the most part subjective; (2) the ingestion or injection of any medicament whatsoever may bring temporary relief, because we must recognize that psychogenic influences often play an important part; (3) spontaneous desensitization to antigens may occur; and (4) the symptoms of allergic episodes are self-limited and may be receding in severity just at the time the drug is tried.

I have read over 100 articles on this subject, and cannot help but feel how wise it would have been if the observations had been withheld for a longer period. A longer experience with these drugs might have given a better perspective. I have tried to be as objective as possible in the perusal of these papers, to present, if possible, an unbiased picture, and have steadfastly attempted to veer away from personal observations in the evaluation of these drugs. It is unfortunate that all of the papers cannot be mentioned, but it would be impractical to cope with them. For the most part they would merely serve to corroborate the viewpoints expressed herein. The literature is already large and new papers are appearing at a rapid rate which is evidence of the great interest which these drugs have aroused.

Judged solely from the literature of the pharmaceutical firms marketing these drugs, they are truly remarkable. The percentage of improvement from their use in the various conditions might be summed up as follows<sup>21</sup>:

Urticaria	95 per cent
Vasomotor rhinitis	77 per cent
Eczema	63 per cent
Hay fever	85 per cent
Asthma	64 per cent
Migraine	66 per cent
Angioneurotic edema	86 per cent
Atopic dermatitis	64 per cent
Pruritus	75 per cent
Erythema multiforme	79 per cent
Dermographia	75 per cent
Food allergy	87 per cent
Contact dermatitis	78 per cent
Physical allergy	64 per cent
Penicillin reactions	97 per cent
Drug reactions	92 per cent
Reactions to biologics	100 per cent
Dysmenorrhea	87 per cent

In published clinical reports, there is wide variance of figures given by the same authors in successive papers.

I confess that I find it difficult to appraise the observations, and must take recourse in presenting the individual evaluation of the various authors, rather than to attempt to make a summation, giving a clear-cut appraisal, as has been done by the pharmaceutical firms.

One conclusion can be drawn. These new pharmaceutical discoveries fall short of the wonder of the newer antibiotic substances, and hence cannot compete with the latter for recognition as truly great advances in medicine. After only one year, we know that these drugs do not cure or eradicate allergy. They are an addition to a long line of palliative remedial agents.

#### DOSAGE

As a rule, benadryl is dispensed in capsules of 50 mg. each, but it may also be prescribed as an elixir, each teaspoonful containing 10 mg. Pyribenzamine is dispensed in 50 mg. scored tablets. Manufacturers advise against biting or chewing the tablets because of the local anesthetic action and bitter taste.

The recommended oral dose for young children is 2 mg. per pound, the total to be divided into two to four doses.<sup>41</sup> The contents of the capsule may be mixed with syrup or jelly. The average dose orally for older children and adults is 50 mg. three or four times daily.

Benadryl has been suggested for intravenous or intramuscular use in solutions of 10 to 20 mg. per cubic centimeter. However, intravenous administration of pyribenzamine is not recommended.<sup>42</sup> Laboratory experiments show that such administration of 1 mg. per kilogram or more in dogs usually results in acute hypotension which lasts for about ten minutes. McElin and Horton<sup>34</sup> found that benadryl given intramuscularly causes pain with erythema, induration, and tenderness.

For nasal use, even a 0.5 per cent solution was found to be too irritating.<sup>33</sup>

These drugs have been given in doses as high as 600 mg. orally per day without obvious ill effect. Curtis and Owens<sup>43</sup> observed three patients who were given benadryl for two, six, and seven months respectively, with no ill effects.

Logan<sup>41</sup> suggests that if no effects are noted in thirty to forty minutes the dose is inadequate and larger doses may be effective. However, I believe that one should be cautious in adopting such a procedure in asthma, for example. It would seem wiser to resort to epinephrine or aminophylline.

The maximum response occurs in about twenty to sixty minutes after oral administration and generally lasts for several hours.

#### URTICARIA

These drugs were first heralded to the American medical profession by Curtis and Owens in 1945,<sup>43</sup> and they were also reported upon clinically in the same year by Shaffer and associates<sup>44</sup> as beneficial in the alleviation of urticaria and angioneurotic edema.

Feinberg and Friedlaender<sup>50</sup> recommended benadryl and pyribenzamine as being equally efficacious in various types of urticarial skin disorders. Where a sedative effect is desired, they suggest the use of the former, and in those cases in which higher doses are needed, the latter. They also noted that relief was obtained by many patients with chronic urticaria in whom other measures failed. In serum sickness following the use of penicillin, the skin lesions were controlled but the joint involvement was not dramatically affected in the majority.

The percentage of good results varies with different investigators, but the majority attest to its value in over 80 per cent of patients suffering from this syndrome. Itching is relieved first, then the swelling and erythema disappear. Often, although the patient is relieved of the itching, the swellings of unusual size still remain.

Schwartz and Levin<sup>51</sup> state that acute wheals disappear within twenty minutes to one hour in their experience, whereas the symptoms can be turned on and off at will by giving or withholding the drug in cases of chronic urticaria.

Logan<sup>41</sup> adds an interesting observation of the effect in a 2-year-old child who had urticaria for three weeks without determining its etiology. After the first dose of 10 mg. the hives disappeared in thirty minutes. The medication was continued for two days and then stopped. For twenty-four hours the urticaria was absent, then recurred, and has since recurred whenever the medication was stopped.

Feinberg<sup>11</sup> further emphasizes this observation by stating that in urticaria and "serum-sickness" reactions the relief is apparent for only a few hours following each dose of the medicament and that the final course of the ailment is in no way shortened or affected by this therapy. One never knows when a spontaneous recession will occur. Barefoot and associates<sup>49</sup> rightly point out that it is difficult to evaluate the therapeutic value of benadryl and pyribenzamine in acute urticaria because many patients would be asymptomatic within a few days without any form of therapy.

These drugs do not eradicate the underlying cause of urticaria, the antigen-antibody interreaction, and episodes do recur. Levin's<sup>45</sup> statement is of interest, therefore. He found that they were excellent for children with acute urticaria and noted that relief occurred as promptly as with epinephrine. Hence, in patients who in the past required several injections per day for several days, they may prove to be a good substitute because they can be administered orally.

Curtis and Owens<sup>43</sup> gave benadryl for periods of two, six, and seven months respectively to three patients with urticaria, without ill effects. They believe that symptomatic relief can be afforded for many months in cases in which the etiologic cause is unknown.

In severe or chronic cases these drugs may be valueless.

Todd<sup>48</sup> has worked out an interesting group of urticarial situations (to which we have added a few) in which benadryl and pyribenzamine may be of benefit:

1. In patients exhibiting generalized nonspecific irritability of the skin, which is sub-clinical but becomes manifest when attempting to do routine skin tests.
2. In maintaining the urticaria patient in comfort for a few weeks until specific desensitization becomes effective.
3. In controlling the urticaria following liver injections and penicillin (orally or by injection) and other biologicals and antibiotics.
4. In controlling urticaria and angioneurotic edema of serum sickness.
5. In relieving both allergic antigen-antibody whealing and nonallergic urticaria.
6. In relieving promptly the whealing reactions to larva migrans, Black Flag, D. D. T., and other insect, parasitic, and chemical irritants.
7. In dermatographism.
8. In poison ivy.
9. In urticarial dermatoses caused by barbiturate compounds and other drugs.
10. In pruritus ani and vulvae.



## SERUM SICKNESS AND ANAPHYLACTIC SHOCK

In serum sickness, the relief is apparent for only a few hours following each dose of these drugs. The itching is relieved promptly and the lesions are kept in abeyance in the majority of cases. It is difficult to ascertain, however, whether the final course of the ailment is in any way shortened or otherwise affected by this therapy.

The value of benadryl in a severe case of accelerated serum sickness is exemplified in a report by Bowen.<sup>52</sup>

A child of 2 years was given 1,500 units of tetanus antitoxin subcutaneously. Forty-eight hours later he had violent urticaria and three days later the edema was so massive, and by the sixth day the respiratory difficulty so critical, that a bad prognosis was given the parents. All emergency measures had been tried, including epinephrine in oil and aqueous solutions and glucose intravenously. At 5 P.M. of the seventh day, when the child's condition appeared hopeless, 100 mg. of benadryl was given by mouth, followed by 50 mg. every four hours for four doses, then every six hours for twenty-four hours. Three days later the child was discharged, completely well.

A 9-year-old female patient experienced an anaphylactic shock reaction in the course of protein skin testing by Drs. Samuel Untracht and Frederick Hertzmark on our pediatric service at Sea View Hospital.

After 0.02 c.c. of horse serum and 0.02 c.c. of dust extract had been given intracutaneously on two separate sites on the forearm, the patient developed an immediate large local reaction at each site. Within a few minutes generalized urticaria spread over the entire body and angioneurotic edema involved the face and upper and lower extremities. This was diagnosed as a systemic anaphylactic reaction to the test materials. Moderate but typical sibilant râles were heard in the chest. The child was given 3 minims of epinephrine five minutes after the reaction. Her condition became progressively worse, with marked itching and exaggeration of the urticaria, and angioneurotic edema completely closed her eyes. Massive edema was evident in her hands and feet. About an hour after the reaction occurred, 50 mg. of benadryl was given. The patient became drowsy within a few minutes. The itching gradually subsided, even though the urticaria became more pronounced, and she appeared comfortable. Two hours later, 100 mg. was administered and the child slept through the night. Benadryl, in 50 mg. doses, was repeated three times a day for the next two days. On the third day the condition had cleared completely.

This dermal type of anaphylactic reaction apparently responds well to benadryl. The fact that 3 minims of epinephrine were given promptly may have altered the respiratory distress. I am not certain whether these drugs would act as brilliantly with a profound bronchiolar spasm characteristic of the guinea-pig type of anaphylaxis. But in our case, as in Bowen's, it certainly appears to have been of value in the edematous type of reaction.

It is interesting in contrast to present the case of a 5-year-old boy in another of our wards who developed an attack of asthma at about the same time as the episode described. When benadryl was administered to him he became drowsy, but progressed rapidly into a state of greater obstruction of respiration. He became cyanotic and appeared critically ill. Oxygen and aminophylline intravenously relieved him. It may be that the true asthmatic symptoms of anaphylaxis will not respond to these newer drugs as well as they do to epinephrine and aminophylline.

## SEASONAL HAY FEVER

The majority of reports appear to be favorably disposed toward the use of these drugs with this syndrome.

Koelsche and associates<sup>53</sup> report 75 per cent of fifty-two patients relieved with benadryl. In a symposium<sup>54</sup> given recently, good results were variously indicated to be between 59 and 75 per cent of cases. Arbesman and associates<sup>55</sup> declare that as many as 84 per cent were benefited by the use of pyribenzamine. Logan<sup>41</sup> had twelve cases during the ragweed season with excellent or good results in nine. Of three with associated asthma, only one was helped. Eyer-man's<sup>47</sup> figure is 67 per cent, and Bowen's<sup>52</sup> 60 per cent. Epstein<sup>50</sup> states that most of his pollen cases were benefited. Bowen had three cases in the mid-ragweed season who were amazingly relieved with benadryl. Feinberg and Friedlaender<sup>56</sup> report 82 per cent of 254 hay fever patients showed benefit.

However, Friedlaender<sup>57</sup> warns that unless rigid criteria are used to evaluate the beneficial results, overenthusiasm is the result. He believes that the majority of hay fever reports to date have not employed the criteria necessary to establish a firm basis for claims. Many unsubstantiated claims have been made in regard to other "cures" in the past, because there is so much dependence on subjective data. Friedlaender's criteria include daily pollen counts, prevailing atmospheric conditions, and control groups; with an evaluation on this basis, he was able to attribute improvement definitely to benadryl in but a small percentage of his cases. Doses of 50 to 200 mg. daily were employed in the majority of cases.

Feinberg<sup>51</sup> and Arbesman<sup>55</sup> suggest that pyribenzamine in combination with ephedrine or aminophylline is more effective. Relief from these drugs is usually noted after the first dose, but often several doses are required.

It has been reported that blockage of the nose is often aggravated by these drugs. They apparently work best in the watery type of hay fever. In patients who have used nasal constrictors too consistently and who have a blocked nose as a result, some have found that pyribenzamine and benadryl sometimes relieve the condition.

## NONSEASONAL ALLERGIC RHINITIS

Reports are not in agreement with respect to the effectiveness of these drugs in nonseasonal allergic rhinitis. At a symposium of the American Academy of Allergy,<sup>54</sup> the reports varied from 28 to 85 per cent effectiveness.

Schwartz and Levin<sup>51</sup> found that either relief is obtained within one hour or no benefit is derived. Once relief is obtained, it is necessary in most cases to continue the drug every four hours because the action is only palliative.

Epstein<sup>50</sup> did not find the drugs very effective in cases due to dust or food sensitivity, and still less so in so-called intrinsic rhinitis in which external allergens cannot be demonstrated.

On the other hand, a report appears by Williams<sup>58</sup> who obtained relief in 90 per cent of ten patients with perennial vasomotor rhinitis. In hyperplastic ethmoiditis he also found a disappearance of polypoid tissue and a diminution of purulent discharge, but indicates that symptoms tend to return within twelve hours of cessation of dosage.

With equal assurance Eyerman<sup>47</sup> indicates that polyposis was not helped, and Bowen<sup>52</sup> states that less than 20 per cent of his vasomotor rhinitis patients, obtained relief.

Arbesman and associates<sup>55</sup> found that pyribenzamine relieved sneezing in rhinorrhea and nasal occlusion in 75 per cent of 313 patients with allergic rhinitis.

Feinberg and Friedlaender<sup>56</sup> noted benefits in 64 per cent of the cases with pyribenzamine, whereas Feinberg<sup>59</sup> observed such benefits in only 15 per cent of forty-seven cases with benadryl.

#### DERMATITIS

One of the admitted virtues of benadryl and pyribenzamine is their effectiveness in relieving pruritus. However, they have their greatest value in the milder forms of dermatitides, not through any curative action, but because the relief from itching and scratching is frequently responsible for some improvement in the cutaneous lesions.

Feinberg<sup>11</sup> found that pyribenzamine relieved itching in sixteen out of twenty patients with acute and chronic atopic dermatitis, while benadryl was effective in twenty out of twenty-five similar cases. Contact dermatitis was less responsive. Waldbott<sup>60</sup> and Levin<sup>45</sup> obtained equally good results. Epstein,<sup>30</sup> however, found it difficult to evaluate their effectiveness in atopic dermatitis, and believed that only acute exacerbations were relieved, but not atopic dermatitis of long standing, contact dermatitis, or infectious eczema. He found that erythema multiforme was benefited. Pyribenzamine was more effective than benadryl in his experience.

Neurodermatitis and dyshidrotic eczema were unaffected,<sup>44</sup> as well as disseminated dermatophytide, severe local reaction to diphtheria toxoid, and pruritus with jaundice.<sup>49</sup>

A definite decrease in itching was noted in certain cases of contact dermatitis and poison ivy. Dermographism was reduced.<sup>11, 52</sup> Bowen believes that where you have edema and pruritus in juvenile eczema these drugs are frequently helpful in allaying pruritus.

#### MIGRAINE

The data with respect to the relief of migraine with these drugs are by no means consistent. Some claim that benefit is derived in allergic headaches, Ménière's syndrome, myalgia, and physical allergy of the head (Williams,<sup>55</sup> and McElin and Horton,<sup>34</sup>). Eyerman,<sup>47</sup> Bowen,<sup>52</sup> and Feinberg<sup>11</sup> find them of questionable value. If relief is to be obtained, at least 50 mg. every two hours are needed.

Levin<sup>45</sup> reports an aggravation of symptoms in two patients from benadryl.

#### ASTHMA

In this disease, which affects the majority of allergic children and adults, these drugs are of little real value. There is not the same consensus as with respect to the relief afforded in acute urticaria, seasonal hay fever, and pruritus.

Friedlaender and Feinberg<sup>33</sup> failed to secure any favorable results in twenty patients treated with benadryl, but observed benefit in two of twenty-five patients treated with pyribenzamine. Koelsche and associates<sup>61</sup> reported four of twelve patients improved. Schwartz and Levin<sup>51</sup> observed relief with benadryl in eight of twenty patients; attacks were diminished in severity, and some were completely improved after one or two days. In some cases patients reported aid from placebos. Bowen<sup>52</sup> found that less than 10 per cent of his patients were aided.

McElin and Horton<sup>24</sup> observed that coughing was made more difficult and the expectorated material seemed more tenacious. Epstein<sup>30</sup> also found the results disappointing with both benadryl and pyribenzamine.

Arbesman and associates,<sup>25</sup> however, claim that pyribenzamine prevented or relieved dyspnea and cough in 48 per cent of ninety-eight patients with asthma.

Waldbott<sup>60</sup> reports a favorable outcome with benadryl in a 7-month-old infant who had severe attacks of asthma occurring every ten days and lasting for ten to fifteen hours. On one occasion the infant was cyanosed and stuporous, with respirations of 80 to 90 and an imperceptible pulse. Attempts to relieve this attack by the usual methods were of little avail. However, a marked change in the child's condition ensued within one-half hour after 50 mg. of benadryl were given orally. The pulse rate dropped to 90 and respirations to 36. On two subsequent occasions the drug produced similarly good results. This author, on the other hand, quotes a patient with urticaria and asthma in which the first dose cleared the urticaria but left the asthma unabated, and cites three patients who developed asthmatic attacks shortly after the ingestion of benadryl.

Levin<sup>45</sup> also noted an aggravation of asthma in 3 per cent of his patients. In one instance, when 50 mg. were given to a patient in the office, a severe attack developed, requiring the administration of epinephrine. Two other patients complained of "choking up" within fifteen minutes, and a fourth patient had a marked aggravation of his attack. This author stresses the fact that asthma if infectious origin was not benefited by benadryl.

While treating patients with active pollinosis with 50 mg. of benadryl three to four times a day, Eyerma<sup>47</sup> noted that seven developed wheezing. Two were relieved with further treatment, whereas five were uninfluenced. He also found benadryl ineffective for severe bronchospasm. In two instances of idiosyncrasy to aspirin, bronchospasm increased and adrenalin was required. Benadryl was not efficient in any severe asthmatic episode, even with the oral administration of 100 mg.

In pollen asthma the nasal symptoms are often relieved but not the chest signs. However, the relief of nasal symptoms sometimes is reflected beneficially on the chest condition. Koelsche and associates<sup>61</sup> also noted improvement of hay fever symptoms but not the associated asthma.

Feinberg<sup>11</sup> obtained only 12 per cent favorable results with benadryl in a series of fifty patients with asthma, mainly of perennial etiology. Pyribenzamine was somewhat more effective than benadryl in 28 per cent of 121 patients with

asthma or allergic bronchial cough. But he points out that whatever benefit was derived from pyribenzamine orally, it was never comparable to the practically complete and rapid relief obtained with epinephrine hypodermically administered. Where relief was given it was usually only moderate. The spasmodic cough was more benefited than the dyspnea. He, too, noted that the asthma accompanying hay fever was seldom prevented by the use of either drug.

A drug that can dry up bronchial secretions and produce suffocation and choking sensations might very conceivably kill a patient if used during status asthmaticus. One can only conclude, therefore, that these drugs should be used with circumspection for severe asthma.

#### TOXIC AND UNTOWARD REACTIONS

Prior to the use of these drugs in the human subject,<sup>14, 15, 19, 20, 31, 62</sup> careful toxicologic studies were performed in albino mice, rats, rabbits, and dogs.

*Toxicologic Studies in Animals.*—The conclusion drawn from these studies was that benadryl and pyribenzamine have a low toxicity and are well tolerated by animals in many times the dosage recommended for man.

Death occurs in 50 per cent of albino mice after an oral dose of 167 mg. per kilogram, and in albino rats after 545 mg. per kilogram. Lethal doses are followed by violent excitement, convulsions, respiratory failure, and death in a few minutes to several hours. Excitement and ataxia occurred after nonlethal toxic doses and recovery followed in one to two hours.

From 10 to 60 mg. per kilogram was given orally to dogs for periods of thirty-seven to forty-nine days. No change was noted in eating habits, weight, blood counts, hemoglobin, or nonprotein nitrogen. No abnormal conditions were observed at autopsy, even after prolonged intake. Koepf and associates<sup>63</sup> gave pyribenzamine to dogs for one year in doses of 50 to 200 mg. daily with no alteration in the hematopoietic system, no impairment of liver or kidney, and no febrile reaction.

*Toxicologic Studies in Human Beings.*—According to some reports,<sup>41, 63</sup> these drugs have been given to human subjects for relatively long periods, 2, 3, 6, and 7 months respectively, without any obvious toxic effects.

Nevertheless, many reports have been made of side reactions that were not encountered in the animal studies. These seem to affect the higher brain centers more particularly. The most common complaint is drowsiness of some degree, which occurs more frequently after benadryl than pyribenzamine, approximately in 50 per cent of the cases with the former and 25 per cent with the latter. It is less marked in infants and children, even with large doses.<sup>41, 45</sup> However, in adults it may assume proportions only second to that from narcotics and anesthesia. Many cases of unconquerable somnolence have been encountered. Bowen<sup>52</sup> reports the case of a patient driving a car who failed to heed a red traffic signal and was arrested for being intoxicated, a "benadryl jag." Collisions with serious mishaps have been reported as a sequel. Slater and Francis<sup>64</sup> published a case report of a near fatal accident in a patient after only one 50

mg. tablet. One story is told of the doctor who took six capsules a day, and one day had to be awakened by a patient in the midst of a conference when sleep overcame him.

The effect of drowsiness is excellent therapeutically in pruritus and hay fever if the drug is given at bedtime. Some of the most beneficent effects must be attributed perhaps to this side effect. But we must recognize that if these drugs are given to an asthmatic they may in certain instances be as dangerous as morphine.

We are told that the drowsiness can be overcome with coffee, caffeine, benzedrine, and ephedrine. If this symptom occurs with each dose, medication may have to be discontinued. In some instances, however, this effect wears off rapidly.

Other side effects are dizziness, weakness, dilated pupils, dry mouth, nervousness, tingling of hands, tinnitus, nausea, vomiting, headache, and mental incoordination. Schwartz and Levin<sup>51</sup> report a patient with the sensation of "walking on air," McElin and Horton<sup>54</sup> report several with difficulty in coordination, O'Leary and Farber<sup>46</sup> report a patient with sensations of syncope. Williams<sup>58</sup> had patients who developed severe vertigo and were unable to continue working, and some mentioned difficulty in focusing their eyes.

Friedlaender<sup>57</sup> notes that pyribenzamine in large doses produces symptoms of cerebral stimulation, i.e., vertigo, nervousness, trembling, and insomnia, as frequently as drowsiness and lassitude.

In spite of the assurance from experimental data with respect to prolonged usage of the drugs without evidence of toxic effects, it appears to me to be too early to state finally that these drugs can be used without ultimate harm, judging from the case reports beginning to appear. A friend of mine who extolled the virtues of benadryl for his hay fever found after five weeks of constant use that he developed a persistent headache which lasted for two weeks. Another young person took forty capsules over a period of three weeks and became so weak that she had to remain in bed for one week and felt groggy and uncertain of herself for a week following her return to work.

*Unusual Side Effects.*—Reports of serious and unusual effects are filtering into the literature. Geiger, Rosenfield and Hartman<sup>65</sup> report a case of a shock-like reaction to benadryl.

A white woman, aged 26, was being treated for a generalized seborrheic dermatitis of unknown origin. After receiving a total of 300 mg. of benadryl over a three-day period, she complained of palpitation, dimmed vision, malaise without drowsiness, and heartburn with nausea. Following the next 50 mg. tablet, the patient was found in bed unconscious, cold, pale, and pulseless. The blood pressure could not be read. Eyes were staring, but the pupils were equal and reacted to light. A solution of 7.5 minims of epinephrine (1:1,000) was given subcutaneously. Within thirty minutes the pulse was palpable, though weak, and the patient responded to painful stimuli. In three hours she was normal, with no recollection of what had happened. The following day magnesium soaks, supportive vitamins, and oral dosage of ephedrine were reinstituted and the patient continued to improve. On the eleventh hospital day the administration of benadryl was resumed, under careful observation. Again after 300 mg. over a period of three days, the patient began to complain of the symptoms noted on the previous occasion. She was somewhat disoriented and excited. The pulse was weak, the skin pale, but the blood pressure was normal. Benadryl was immediately discontinued and within two hours the patient felt entirely normal.

*Unusual Symptoms of Cerebral Stimulation.*—Symptoms of cerebral stimulation have been observed, such as difficulty of coordination,<sup>34</sup> muscular twitching,<sup>60</sup> narcolepsy, confusion, jitters, irritability<sup>45</sup> from benadryl, and vertigo, nervousness, trembling, and insomnia from pyribenzamine.<sup>57</sup> All are strikingly exaggerated in a case recounted by Weil.<sup>66</sup>

Benadryl was given for the relief of hay fever to a white boy, aged 3½ years, weighing 33 pounds. He had 50 mg. every morning and at bedtime for three days. On the third day he received 50 mg. just before he was put to bed. He went to sleep and his attitude was considered normal by the parents. At midnight the child awakened with a severe sneezing attack. He was given 100 mg. of benadryl and returned to bed. Twenty minutes later the child was sitting up in bed, singing, laughing, and "starry-eyed." He did not obey requests to lie down and to be quiet, but instead laughed and "acted as though he were drunk." At this time, muscular twitchings of the face and involuntary spastic movements of the extremities were first observed, and urinary incontinence followed. In about ten minutes (by which time Dr. Weil was in attendance) the involuntary muscular movements of the face and extremities were more pronounced and the child was irrational, not knowing where he was and not recognizing his parents. At this time he "dove from his bed to the floor." Although he landed on his head, he laughed as he was picked up and put back to bed. Physical examination was negative, except for: (1) muscular twitchings and purposeless movements of the extremities; (2) hypertonic patellar and triceps reflexes (corneal, cremasteric, and abdominal reflexes were considered normal); and (3) irrational speech gradually becoming slurred. Second, 1½ grains (0.09 Gm.), was administered by mouth, and within fifteen minutes the child was sleeping fitfully. Muscular twitchings and athetoid movements continued, and on moments of awakening the speech was slurred past the point of understandability. On several occasions in the next three hours the child attempted to "dive" out of bed again. About 4 A.M. the child sat up and spoke clearly but still showed evidence of muscular spasm and hypertonic reflexes. He fell asleep again and slept fitfully until 9 A.M. The effects of the second (?)—sleepiness, unsteadiness and anorexia—were evident until after the 2-to-4 P.M. nap. At 4 P.M., the child was examined again and considered normal. The reflexes were normal and conversation was rational. He had no recollection of the activity of the evening and early morning.

Again emphasizing the danger of marked mental disorientation from large dosage, particularly if self-medicated, is the case described by Borman.<sup>67</sup>

A convent nun, aged 18, suffered from ragweed sensitivity. She was given a prescription for forty-eight 50 mg. capsules of benadryl. She was decidedly relieved by them and consumed forty during the following forty-eight hours, a total of 2,000 mg. She became drowsy and acted queerly and disoriented. She dropped clean clothes into the laundry, left her tasks only partially completed, wandered off into other parts of the convent and did not remain in her bed at night. During instruction period she asked one of the sisters to pass the salt. For two nights she had "suffocating spells." Upon examination, her pulse, temperature, respirations, and blood pressure were normal. Within forty-eight hours after discontinuing the drug she made an apparently complete recovery.

To be sure, it may be claimed that the toxic effects herein described are not foreign to many good and valuable drugs, but such drugs are usually used for specific episodes over a definite period. My anxiety is due to the fact that here are drugs which are being prescribed not for a particular illness but for repeated use to relieve allergic symptoms which recur from time to time over many years. It has been amply demonstrated that their effect is purely palliative. The side effects might unquestionably result in accidental death. I have no doubt that

cases have already occurred. Take, for example, the child who runs out into the street after taking the drug; with judgment gone he might easily be run over. An individual in swimming might conceivably be so overcome by drowsiness as to drown. The child who "dove" off his bed, might with equal readiness dive out of the window. The nun walking in her sleep might be exposed to some precarious situation. A drug that can disorient an individual is certainly one to be used with caution.

#### COMMENT

The discovery of a single agent to combat the bewildering kaleidoscope of symptoms inherent in the allergy pattern has been the aim of chemists and pharmacologists, and the desire of practicing physicians.

Hay fever, asthma, urticaria, and eczema are but a few of the varied ways in which allergy manifests itself. The precipitating causes are even more numerous than the symptoms if one lists the foods, weeds, epidermals, drugs, bacteria, textiles, dusts, and organ products that have been found to be responsible offenders. The physician had to become so skilled in ferreting out these initiators of allergic symptoms that a new subspecialty of allergy has been developed in the fields of pediatrics, medicine, dermatology, and otolaryngology. It is to the "allergist" that physicians and patients turn for help in exploring this maze of cause and effect. After painstaking search the patient is taught the substances to avoid, and how to substitute harmless forms for the offenders, and in order to combat the onslaught of pollens he is compelled to take frequent desensitizing injections of the particular pollens to which he reacts.

Now, with the advent of the so-called antihistaminic drugs, the question arises, as to whether the procedures outlined are correct. Is there a drug that will dispel our allergic problem? Is that drug benadryl, pyribenzamine, or some one of the other new antihistaminic drugs which will undoubtedly be put out in competition? The underlying problem, of course, is this: has the histamine theory revealed the basic cause of allergy and given sharper definition to the universal pattern of allergy which is pointing the way to better treatment?

On the one hand, some believe that the major role in allergy is played by the interaction of antigen and antibody on sensitized tissue.<sup>10</sup> Others hold that the release of histamine is the direct and major cause of the allergic phenomenon. Dale<sup>65</sup> was the first investigator to voice this theory. He stated that anaphylactic shock is a result of cellular injury due to the intracellular reaction of antigen with aggregating antibody in the course of which histamine is released. To this released histamine he would attribute the symptomatology.

Dragstedt<sup>4</sup> contends that the pure cellular theory has no satisfactory explanation for the mechanism by which the antigen-antibody reaction produces the phenomena of anaphylactic shock. It seems to me that the proposition, first pointed out by Simonds and later supported by Wells, that the dominant symptoms in anaphylaxis, i.e., circulatory failure in the dog, bronchospasm in the guinea pig, cardiovascular failure in the rabbit, can all be brought into concordance on the basis of spastic contraction of smooth muscle in the various organs in which the sessile antibodies are found in greatest concentration.<sup>10</sup>



The question has been posed, how does the antigen-antibody reaction make the smooth muscle contract? One could counter by asking how does histamine make the smooth muscle contract. As a matter of fact, smooth muscle does contract when subjected to any one of many varied types of stimuli such as chemical and mechanical irritants, temperature changes, and reaction patterns established as "conditioned reflexes," as well as to antigen-antibody interaction or histamine. It is the nature of smooth muscle fiber to contract whenever stimulated; it can do nothing but contract and relax; such is its function.

Code<sup>6</sup> has suggested that histamine is liberated as a consequence of damage done within the sensitized cells, and it is this damage to the cell that is the fundamental etiologic factor in allergic or anaphylactic reactions. Liberation of histamine may be purely incidental. If the damaged cell happens to contain histamine, it will be liberated during the reaction. It must be conceded that if histamine is present in excessively large amounts it may contribute to the intoxication of the anaphylactic animal. However, the reaction takes place so rapidly as a rule that it is hard to believe that histamine can be liberated in sufficient quantity to account for immediate severe allergic reactions or anaphylactic death. On the other hand, Code<sup>6</sup> has shown that histamine is present in the blood of a dog in anaphylactic shock but it disappears after a relatively short time. It is difficult, therefore, to hold the histamine responsible for the anaphylactic death which may occur hours later when histamine is no longer demonstrable.

Actually, histamine release has not been demonstrated in allergy in man to the full satisfaction of all investigators. As a matter of fact, it has only been demonstrated in dogs and guinea pigs in severe anaphylaxis, but not in the rabbit, horse, or calf.<sup>10</sup>

To my mind, the asphyxial symptoms of asthma and a multitude of the minor allergic manifestations can be accounted for more plausibly by the disturbance of the physiology of a vital organ brought about by smooth muscle contraction which results from antigen-antibody interaction.

Where the stress is laid is a matter not only of academic but also of practical importance. To concede the value of a drug, such as benadryl or pyribenzamine, because it allays the symptoms of itching or a watery nose, is one matter. To accept drugs as important contributions in the fundamental treatment of allergy because they are said to be antihistaminic can only mean that we are ready to believe that histamine is the cause of allergy. The fact that these drugs relieve symptoms, as has already been said, is not conclusive proof that these symptoms are due to histamine. For my own part, I feel that we will require further and more convincing proof before such a conclusion may be drawn.

Much as we would desire it, I cannot conceive of a universal cure-all in allergy. The very nature of allergy, and its underlying antigen-antibody mechanism, precludes it. Were we to discover how to prevent the development of allergic antibodies, the problem would be settled. But the essence of allergic antibodies is the very essence of all antibodies. A substance that would

destroy all antibodies would obviously lead to a state incompatible with survival against noxious invading substances. The body must continually manufacture immunizing agents. The amelioration of allergy is based on the ability of the body to produce enough antibodies so that they may eventually reach the circulation and act as blocking or neutralizing bodies. Allergy is an ever-present battle against all types of foreign substances inhaled, ingested, or injected.

It is the study of the many ways and means that antigens have of invading the body and producing inter-reactions with tissue antibodies which offer the greatest hope for good and lasting results. The therapy of allergy must be viewed from a constitutional and preventive standpoint. It entails a search for all offending substances, their elimination or reduction, and a definite program for building up tolerance. The control of environmental excesses, highly antigenic food excesses, promiscuous and thoughtless use of sera and drugs, control of diseases which tend to increase the permeability and dysfunction of our protecting membranes, all tend to reduce the incidence of allergy. The problem rests heavily with the pediatrician because most allergies start in childhood. Don't think there is a short cut. For the present, there is no single drug or procedure that can do more than allay certain minor phases of the allergic symptomatology. Once the mechanism of a disease is understood, amelioration and possible eradication eventually follow. Were we to accept the histamine concept as the primary *modus operandi* of the allergic reaction, as I see it, there would be little hope for the control and prevention of allergy.

#### CONCLUSIONS

1. The release of histamine has not yet been proved to be the fundamental factor in anaphylaxis or allergic reactions, hence any therapy based on such a concept must be called into question.

2. Benadryl and pyribenzamine and other drugs of this group have not been proved to be antihistaminic, either chemically or pharmacologically.

3. These drugs have not proved of value in the eradication of allergic syndromes. They do not appear to prevent the entrance of antigen into the circulation and the antigen-antibody reaction from ensuing.

4. It is the nature of the allergic episode to be self-limited, and it is often spontaneously terminated without benefit of medical intervention. For this reason a wide variety of drugs seem to relieve it.

5. Benadryl and pyribenzamine are excellent compounds which alleviate symptoms of a widely diversified group of allergic conditions. It is significant that the greatest benefits are derived in acute urticaria and hay fever, in allaying pruritus, nasal and lachrymal discharges. They should take their place along with epinephrine, ephedrine, and atropine as excellent antispasmodics.

6. They are not as efficient in asthma and eczema, the more chronic and fixed syndromes, and should be used cautiously in the former.

7. These drugs must be used vigilantly because they may have serious side effects which in some cases may affect the higher brain centers.

8. These drugs deserve a place in our armamentarium as symptomatic remedies. My objection is that many physicians and more particularly lay

people, because of the widespread publicity, feel that they are cures. Furthermore, I feel that if we lay emphasis on palliative measures we will forget what is more important—that is, measures seeking to overcome the actual hypersensitivity of the patient. It is more important to look to the fundamental and basic principles underlying allergic phenomena, than to be content with mitigating measures. The latter may have a place during the period of investigation and initial treatment of a case, but certainly we should not be satisfied with that limited aim.

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## GENITOURINARY CONDITIONS IN INFANTS AND CHILDREN

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UROLOGY as a specialty began when Max Nitze paved the way to more precise urologic diagnosis with his invention of the cystoscope. The progress of urology can be divided into the precystoscopic and cystoscopic eras, which enabled one to pass from speculative or theoretical views to one of accurate diagnosis.

The application of the knowledge gained in the development of urology lagged in the field of pediatrics for the following reasons: (1) for the want of small instruments and not because similar conditions were not found in the young; (2) the sentimental objections to the use of the cystoscope and instrumentation in these little patients; (3) the lack of knowledge that complete urologic study was possible in infants and children; (4) the failure of both pediatrician and general practitioner to utilize modern methods of urologic diagnosis; (5) lack of cooperation between pediatrician and urologist, the former treating the child medically or expectantly with the hope that the condition would clear up, the result being that by the time the case reached the urologist, irreparable injury had been done to the upper urinary tract; and (6) the urologist rarely had the first opportunity to examine and study these patients.

In general, many of these statements have undergone great changes. Instead of these patients being seen with far-advanced lesions, they are referred for study at a much earlier time. Unfortunately, some of the above statements still hold true. On the other hand, the keenly alert pediatrician is fully aware of them. For example, some of these patients with so-called pyelitis have been referred to me at as early as 2 months of age.

Urologists, in this country more than any other, have taken a keen interest in the subject of urology in children. Their continuous interest in seeking smaller and better instruments, as well as in diagnosis and treatment, stands in marked contrast to the European urologists, whose efforts have been sporadic.

### THE EVOLUTION OF SMALL UROLOGIC INSTRUMENTS

It is extremely interesting to review the development of small urologic instruments and the role played by urologists of this country in their perfection. It is a far cry from Nitze's statement that cystoscopy was not possible in boys under 10 years of age. Age is no longer a contraindication. I have examined a boy 7 days old with a cystoscope.

As early as 1902, Berliner diagnosed a hemangioma of the bladder in a female, 11 years of age, with the cystoscope. In 1908, Portner described a child's observation and catheterizing cystoscope. Bacharach, in 1910, diagnosed

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telangiectasis of the bladder in a girl of 13 years by cystoscopic examination. Casper and Jacoby, in 1911, each described a cystoscope that could be used in children.

To the late Edwin Beer of New York belongs the credit for developing the first practical catheterizing cystoscope to be used on children, which he described in 1911. The youngest girl on whom Beer used cystoscopy was 14 months of age and the youngest boy was 5 years old. The youngest patients whose ureters he catheterized were a girl of 5 years and a boy of 10 years.

In 1924, Butterfield constructed a double catheterizing cystoscope of 16 F. caliber, and in 1930 he described a new baby cystourethroscope for purpose of examination, catheterizing the ureters, and which also permitted the use of the fulgurating current. In 1929, McCarthy presented his miniature cystoscopic outfit. Corbus, in 1930, described a children's observation, irrigating, and catheterizing cystoscope less than 11 F. in caliber. In 1932, Sprenger brought out a single catheterizing cystoscope of 10 F. caliber and Young presented his new double catheterizing cystoscopes for adults and infants. In 1936, Campbell's universal miniature cystoscopic outfit was evolved.

In the discussion of the role played by the urologists of this country in the development of small efficient instruments, great credit must be given to the Wapplers for their untiring energy, ingenuity, and unending enthusiasm for aid and cooperation.

#### THE GROWING CONSCIOUSNESS OF THE APPLICABILITY OF THESE INSTRUMENTS

In addition to those interested in the development of these small instruments, many others are to be given credit for their readiness to accept and apply the instruments, and to stress repeatedly the value and feasibility of employing them in infants and children.

As early as 1917, Quinby directed attention to cystoscopy and ureteral catheterization in children. From then on there is a steady and continuous stream of contributions by Beer, Bugbee, Campbell, Hinman, Hyman, Kretschmer, Mertz, Schmidt, Stevens, and many others too numerous to mention here, who emphasized that no longer can age be used as an alibi against complete urologic examination in infancy and childhood, as in general the indications and contraindications for cystoscopy in children and adults are identical.

This increasing enlightenment in the realm of pediatric urology has helped to alleviate suffering in the young and prevent much unnecessary invalidism in adult life. Diagnosis is made early, proper treatment is instituted, and better results are obtained.

#### ANOMALIES OF THE URINARY TRACT

Since the advent of modern urologic diagnosis, and especially since the routine use of intravenous urography, the old idea that congenital anomalies of the urinary tract are rare has been completely disproved. It is surprising how frequently renal anomalies are found.

It is to be emphasized that the mere presence of an anomaly does not indicate surgical intervention unless the anomaly has produced changes; for example, stone, hydronephrosis, and recurring attacks of pyelonephritis. Then, too, it should be borne in mind that the symptoms attributed to the anomaly may be due to some other condition, and operation under these circumstances would fail to relieve the patient of the symptoms.

Abnormalities of the urinary tract assume clinical significance when pathologic processes develop in them. It is believed by some that the anomalous kidney is more likely to be the seat of disease than the normal kidney. The mere presence of an anomaly does not indicate that symptoms will occur because of the anomaly itself. Congenital anomalies of the urinary tract not infrequently produce interference with urinary drainage so that stasis results, and sooner or later infection intervenes and medical management has no effect on the condition.

Helmholtz, many years ago, stated that when pyuria persists longer than four or six weeks despite intensive medical therapy, a complete urologic examination should be carried out. It is interesting to note the frequency with which congenital anomalies are found in patients with persistent pyuria and in patients with relapsing pyelonephritis who fail to respond to efficient medical treatment.

Lowsley and Butterfield, in 1926, reported 100 cases of urologic conditions in children and found twenty-nine congenital anomalies; thirteen of such a nature as to predispose to infection of the urinary tract. In 1928, Mertz reported twenty patients with persistent pyuria in which the basis was congenital anomalies. In 1937, I found that twenty-four of my 101 reported cases of hydronephrosis were associated with congenital anomalies of the kidneys and ureters, and sixteen cases (40%) of hydronephrosis were associated with obstruction at or in front of the bladder neck.

These figures are not to be construed as to the frequency of the occurrence of anomalies, but only to indicate how frequently they are present in patients with chronic pyuria and relapsing pyelonephritis.

It is well known that children, as well as adults, often present themselves with obscure intra-abdominal symptoms, when the symptoms are due to overlooked urologic conditions. It is perfectly obvious that these patients should have the benefit of complete urologic study. My experience in this group of cases coincides with that of Mertz and Hamer. In studying 167 children over a period of five years, they found that the most frequent clinical manifestations of an upper urinary tract anomaly were chronic pyuria with or without fever, abdominal colic, and abdominal tumor.

*Bilateral Renal Agenesis* is of no clinical interest because the condition is incompatible with life.

*Supernumerary Kidney.*—True supernumerary kidney is among the rarest of all renal anomalies. I reported a case in 1915 and another in 1929 together with a review of twenty-nine cases from the literature. The largest number of supernumerary kidneys occurred in the second decade of life. The only reported



case of this anomaly in a child was reported by Pick (quoted by Neckarsulmer), as found at autopsy in a girl, aged 9 months. A recent paper by Carlson states that only forty-six cases of supernumerary kidney have been found up to 1946.

Because of its great rarity and because it is discovered in the adult, it has little interest for the pediatrician. Unfortunately, many cases of double kidney pelvis have been reported as supernumerary kidney. This is careless medical speech. Some patients have been told they had three kidneys because they had a double kidney.

*Simple Renal Ectopia or Dystopia.*—Although the number of cases reported in adults increases from year to year, the number found in children is very small. I have never seen a child with this condition who had symptoms and required treatment. It seems to be fair to assume that this congenital anomaly does not begin to produce symptoms until adult life. However, the possibility of its occurring in children should be borne in mind. Its presence is readily demonstrable by urologic examination.

*Solitary Kidney* may be recognized at any age. The symptoms of a diseased solitary kidney are no different than when two kidneys are present. Symptoms may be pain, hematuria, pyuria, or anuria, and it is important to utilize all modern diagnostic methods so that the solitary kidney can be recognized and conservative surgery employed and not err in removing the solitary kidney.

Because only one kidney can be demonstrated by intravenous urography, one must not assume that we are dealing with a case of solitary kidney. A 5-year-old boy referred to me with a diagnosis of solitary kidney made from the intravenous urogram, showed on retrograde pyelogram a small, congenital, hypoplastic kidney without function which had no visualization in the intravenous urogram.

*Horseshoe Kidney or Fused Kidney.*—I have seen but one child with fused kidney. This condition can be readily recognized in the plain roentgen film and in the pyelogram. It is important because of its susceptibility to infection and stone formation, due to its anomalous position, the anomalous blood supply, and the course of the ureters, all of which interfere with drainage.

Although a great many articles dealing with this subject are found, few deal with children. Some of the earlier American reported cases of horseshoe kidney in children are: Hand's two cases in 1898; Caverly's report in 1904; Eisendrath's case in 1912; and Thompson's case in 1913. Bugbee and Wollstein, in 1924, in 4,903 autopsies in children, found three cases of fused kidney. In Campbell's series of 12,080 pediatric autopsies, the incidence was 1:335. He found this anomaly twice in over 700 children subjected to pyelography and in one of these cases the condition was recognized only at operation. Mertz and Hamer, in 1938, discovered three instances in 167 patients.

It appears that this lesion does not become the seat of disease very frequently in children.

Unilateral fused kidney with ureteral reduplication is rare. Up to 1941, only six cases had been reported; three of these occurred in children and were reported by Wilcox in 1921, Hess in 1923, and Bugbee in 1924.

*Renal Hypoplasia* results from congenital failure of development, and is often associated with other abnormalities. There is comparatively little written on the subject. The clinical importance of this anomaly is that the small amount of renal tissue present, when bilateral, is not sufficient to sustain life. The hypoplastic kidney is more subject to infection than a normal kidney. This condition has been frequently associated with hypertension, and urologists many years ago recognized that when the hypoplastic kidney was removed, the hypertension disappeared, and the blood pressure returned to normal or nearly normal.

In 1942, Powers and Murray reported on a boy, aged 6, who had hypertension associated with aplasia of one kidney, which was relieved by nephrectomy. Their survey of the literature disclosed fourteen American cases in whom juvenile hypertension was associated with unilateral renal disease which was relieved by removal of the affected kidney. Higbee, in 1944, reported an interesting case of a child aged 12, who had a congenital renal hypoplasia associated with hypertension.

E. S., aged 4, was admitted to the Presbyterian Hospital Sept. 14, 1946, and discharged Sept. 22, 1946.

The patient had had many attacks of fever associated with pus in the urine. Two months before admission to the hospital, his mother discovered gross blood in the urine. Large clots were passed with the urine. The hematuria continued for two days. Following this attack of hematuria, the child developed frequency of urination and dysuria. At this time he had a temperature of 103° F. The temperature gradually came down and was normal at the end of two weeks.

Physical examination of head, eyes, ears, and nose was negative. Examination of throat showed slight enlargement of tonsils. Heart, lungs, abdomen, and external genitalia were negative. Central nervous system was negative. Blood pressure was 118/78. Examination of blood on Sept. 15, 1946, showed hemoglobin, 12 Gm.; red blood corpuscles, 4,790,000; white blood corpuscles 15,400. Examination of urine showed albumin, sugar, casts negative; one or two red blood corpuscles to the high power field; no pus cells. Nonprotein nitrogen was 45 mg. per cent; albumin globulin was 1.53; total protein was 8.22. X-ray was negative for stone. Intravenous pyelogram showed right kidney to be normal; there was no visualization on the left side. Cystoscopic examination was made elsewhere; the bladder was normal. Retrograde pyelogram was made on the left side. The pyelogram was compatible with and typical of a hypoplastic kidney.

Operation was done Sept. 16, 1946, with ether anesthetic. Left nephrectomy was done by H. L. K. The patient made an uneventful recovery and left the hospital on the sixth day.

Pathologic report by Dr. George M. Hess gave a diagnosis of: congenital malformation of left kidney; congenital hypoplasia of left kidney; and slight, chronic pyelonephritis.

*Double Kidney and Double Ureter.*—Formerly considered very rare in both children and adults, the routine use of intravenous urography has demonstrated that they occur quite frequently and are often found without their presence being suspected. Here again, it would be well to emphasize the fact that the mere presence of this anomaly is no indication for operation. On the other hand, in patients with chronic pyuria, hydronephrotic changes in one half of the double kidney, and recurring attacks of pyelonephritis, nothing short of heminephrectomy will effect a cure.

The condition may be unilateral or bilateral and may be associated with reduplication of the ureter. Ureteral reduplication may be unilateral or bilateral, complete or incomplete. The two ureters may fuse anywhere from just below the renal pelvis to just outside the bladder. Where the two ureters fuse outside the bladder, there are two ureteral orifices in the bladder. This is the more common type of reduplication. Where the reduplication is complete, there are, if unilateral, three ureteral orifices in the bladder, and, if bilateral, four.



Fig. 1.—Congenital hypoplasia of the kidney with chronic pyelonephritis.

As a rule, the upper half of the double kidney is the one harboring the pathologic lesion. I have seen only one patient in whom the lower half of the double kidney was the seat of extensive hydronephrotic atrophy. Fortunately for these children, the upper or rudimentary half is diseased, which makes its removal simple, and one is able to save the lower and, incidentally, the larger half.

The operation of heminephrectomy is a simple one, and the results are most spectacular.

*Polycystic Kidney.*—Polycystic renal disease is often hereditary and is characterized by the formation of cysts within the parenchyma, which results in the surface of the kidney being studded with small cysts. The exact incidence of this disease is unknown, as statistics of various authors differ considerably. There are not too many reported cases of this condition in children, which is probably due to the fact that many times the condition is not recognized during life, and clinical manifestations in the majority of patients with this disease do not appear until adulthood.

I have seen two cases of polycystic disease in children. In one, the kidneys were normal in size and had not yet reached the typical cyst formation, so that the surface of the kidneys was smooth. In the second, the kidneys were enormously enlarged and many cysts were found. This case is to be reported in detail at a later date.

Campbell has seen forty-eight cases in children at necropsy. Yardumian and Ackerman, in 1943, reviewed ten cases of congenital polycystic kidney from the Montefiore Hospital; one of these concerned a newborn infant. H. C. Shands, in 1945, reported three infants who had simultaneous occurrence of polycystic kidneys and erythroblastosis fetalis. Roos, in 1941, reported a bilateral polycystic kidney in a girl of 5 months. In 1945, Smith and Graham published a case of a child, 8 years old, with congenital medullary cysts of the kidneys with severe refractory anemia. No other members of the family were known to have had polycystic kidneys.

*Solitary Cysts of the Kidney* are rare in children. Chalkley and Sutton, Jr., in 1943, published a personal case of an infected solitary cyst of the kidney in an 11-year-old child. In their review of the literature, they were only able to gather ten cases of solitary renal cysts in children.

Braasch and Hendrick, in 1944, reported that simple renal cysts were observed in only four patients under 21 years of age, two of whom were infants, 8 and 15 months old.

*Ectopic Ureteral Orifice.*—Closely associated with the subject of ureteral reduplication is the abnormal insertion of one of the ureteral orifices outside the bladder. In the female, the ectopic orifice may be located in the urethra, generally on the floor. It may be located to one side of the external urethral orifice or below it, in the vagina, or in the uterus. In the male, the ectopic opening has been found in the prostatic urethra, the prostate itself, in the seminal vesicle, or in the vas deferens.

It occurs more frequently in the female than in the male, and is often overlooked for many years. All but one of the cases of ectopic ureter that I have seen have been cases of double ureter. The one exception occurred in a woman, aged 21, in whom both ureters terminated in the urethra (reported with Heaney in 1929).

As a rule the ectopic ureter drains the upper half of a double kidney. As a result of this anomaly this half of the kidney undergoes hydronephrotic atrophy and frequently is infected.

A tentative diagnosis can almost always be made from the history. A careful history will elicit the fact that the patient is "wet all of the time," losing urine continually, day and night, irrespective of the act of micturition. This fact should at once arouse suspicion of the presence of an ectopic ureter. Unfortunately, this condition is all too frequently diagnosed as enuresis.

Some patients have had many cystoscopic examinations, including several sets of retrograde and intravenous pyelograms, and have had all sorts of treatments for many years without any influence on the symptoms, due to the fact that the cause of the symptoms was not recognized.

The diagnosis is made by finding the ectopic ureteral orifice, which can readily be located in girls with a good exposure, proper light, and a discerning eye. The intravenous urogram is often helpful. It shows the presence of a double pelvis and two ureters. If the upper half of the double kidney has undergone hydronephrotic atrophy, there is no visualization of the upper half. However, the configuration of the urogram is most suggestive.

The treatment is heminephrectomy.

L. S., a single woman teacher, aged 27, consulted me on June 18, 1935.

The previous history is irrelevant. The patient has had many urologic examinations and treatment without relief of her complaint. Her present complaint was inability to hold her urine. She stated she had incontinence as long as she could remember, and had been obliged to wear a napkin night and day because of her condition. She had no burning, urgency, hematuria, pain, or frequency. She stated that she voided normally.

On the floor of the urethra just behind the external urethral orifice was seen an opening from which urine was emitted. A ureteral catheter was passed into this opening and a retrograde pyelogram was made.

Cystoscopic examination June 24 showed the bladder and ureteral orifices to be normal. Retrograde pyelograms were normal. The pyelogram made with a catheter in the aberrant orifice showed a great deal of dilatation of the calyces and dilatation of the ureters. Examination of the urine was negative. The urine was sterile on culture.

Blood count, blood pressure, and blood chemistry were normal.

A diagnosis of double kidney with complete reduplication of ureter, one of which was ectopic with hydronephrotic atrophy of the upper half of the double kidney was made, and operation was advised.

Operation was done June 26 with ethylene anesthesia. It was a right heminephrectomy. The upper embryonic half of the kidney was small. It was soft, due to hydronephrotic atrophy. The embryonic half had its own blood supply. The patient made a smooth and uneventful convalescence and was discharged July 13, 1935.

*Ureterocele.*—This condition is sometimes called cystic dilatation of the lower end of the ureter. Although it is relatively uncommon, it occurs frequently enough to bear its possibility in mind. This lesion is important because of its devastating effect on the kidney.

According to Hinman it is of two types: (1) a ballooning out of the vesico-ureteral mucosa because of a narrow, constricted ureteral meatus and (2) herniation of all the layers of the ureteral wall into the bladder.

Because of the interference with drainage, hydronephrosis is always present. When infection is superimposed, the patients have chills and fever with a marked pyuria. As a result, a diagnosis of pyelitis is made, and the patient is given medical treatment for long periods of time, to no avail.

The ureterocele may be unilateral or bilateral, and may vary greatly in size. In some cases the ureterocele protrudes from the external urethral orifice.

The diagnosis is readily made upon cystoscopic examination which shows a rounded, semitranslucent swelling covered with smooth pink mucous membrane. When the ureterocele is large it may produce obstruction to urination, thus resulting in hydronephrosis. A characteristic picture is obtained in the cystogram obtained with intravenous urography. This shows the presence of a large filling defect in the cystogram (Fig. 3).

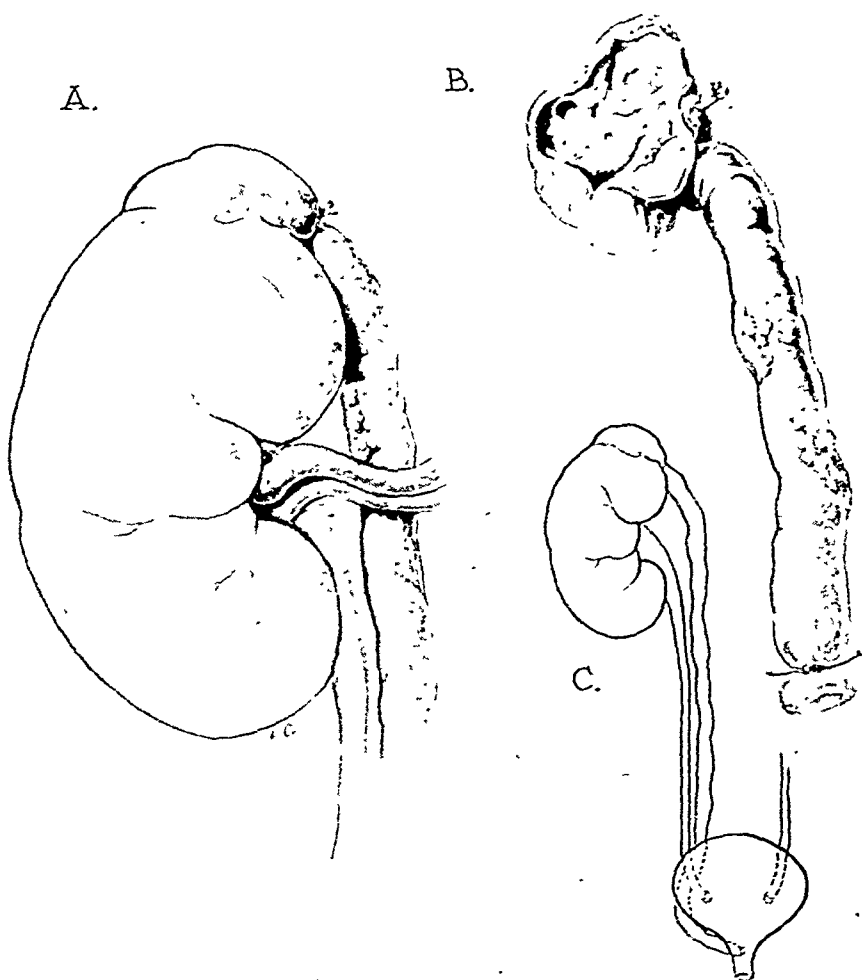


Fig. 2.—A, Double kidney and ureter; B, almost complete hydronephrotic atrophy of the rudimentary upper half of the kidney; C, termination of the aberrant ureter in the urethra.

A ureterocele may be found at the end of a single ureter and if the condition goes unrecognized for a long time the changes in the kidney may be so far advanced that nephrectomy may be necessary. When the ureterocele occurs at the end of a reduplicated ureter, heminephrectomy may be indicated. The

ureterocele is best and easiest treated with the high frequency spark or by resection with the resectoscope. In all of the children I have seen the condition fortunately was found at the end of an accessory or double ureter, so that only the upper half of the double kidney had undergone hydronephrotic atrophy with severe secondary infection. Heminephrectomy resulted in a complete cure.

N. L., aged 20 months, was admitted to Presbyterian Hospital Sept. 23, 1945.

The mother stated that since birth it had been apparent to her that the child had pain on urination. The child held her urine as long as possible and screamed while passing urine.

Examination of the urine prior to admission to the hospital showed pus and albumin on several occasions. The child was referred for diagnosis and treatment.

Physical examination was completely negative. Blood examination was normal. Examination of the urine showed acid: albumin 1+; casts, none; and many leucocytes. Blood chemistry on Sept. 25, 1945, showed urea nitrogen 12 mg. per cent; uric acid 3.2 mg. per cent; creatinine 1.3 mg. per cent; nonprotein nitrogen 38 mg. per cent. There were 12,800 leucocytes per cubic millimeter. Culture showed a luxuriant growth of *Escheria coli communis*.

Roentgen ray examination September 24 showed no stone shadow. Right pyelogram showed dilatation of pelvis, calyces, and ureter. Pyelogram on left side showed an enlarged kidney; pelvis and calyces were normal. A large, round, filling defect was seen on the base of the bladder (Fig. 3). Cystoscopic examination showed the presence of a large, smooth, round swelling covered with mucous membrane. Because of the large size of this swelling, it was impossible to locate the ureteral orifices. Diagnosis of cystic dilatation of the vesical end of the ureter was made. Bipolar fulguration was carried out on September 25.

A second pyelogram on Oct. 1, 1945, was made before the child was discharged from the hospital. The previously seen dilatation of the right ureter returned to normal in this short period of time, six days after fulguration. Because of the large outline of the kidney on the left side, a tentative diagnosis of double kidney with no visualization of the upper half was made. Because of the dilatation of the right ureter, the impression was gained that the cystic dilatation of the ureter was right sided. Subsequent events proved that the cystic dilatation took its origin from the left side. It is interesting, therefore, to note that although the cystic dilatation was left sided in origin, it resulted in a hydroureter on the right side.

The patient was brought back to the hospital for cystoscopic examination Nov. 24, 1945. Ethylene anesthesia was used. The child strained a great deal and a large mass of tissue protruded from the external ureteral orifice. This had the appearance of the cyst which was fulgurated previously. It was grasped with an artery forceps and pulled out as far as possible and cut off with the fulgurating current.

The mother was instructed to bring the child back for further observation and the child was admitted again to the Presbyterian Hospital on Sept. 17, 1946.

Physical examination was negative. Blood count was normal. Examination of urine: cloudy; albumin; many pus cells; many bacteria; leucocytes, 18,000 pus cells per cubic millimeter.

Cystoscopic examination on Sept. 18, 1946, showed the right ureteral orifice to be normal. On the left side were seen two ureteral orifices; one was normal, the other was dilated. Both left ureters were catheterized and a set of retrograde pyelograms were made with the following report (Fig. 4): double kidney with double ureter; and hydronephrotic atrophy of the upper half. Operation was advised.

Heminephrectomy was on September 18, with ethyl chloride anesthesia. The ureter from the lower or large half was normal. The ureter from upper or embryonic half was very much enlarged and its walls were thick. The lumen and pelvis were dilated. There was almost complete hydronephrotic atrophy (Fig. 5). The child had a smooth and uneventful convalescence and was discharged Sept. 27, 1946.

*Congenital Stricture of the Ureter.*—In some cases of large hydronephroses, especially early in life, a diagnosis of congenital stricture of the ureter at the



Fig. 3.—Large filling defect in the cystogram due to the uterocoele.

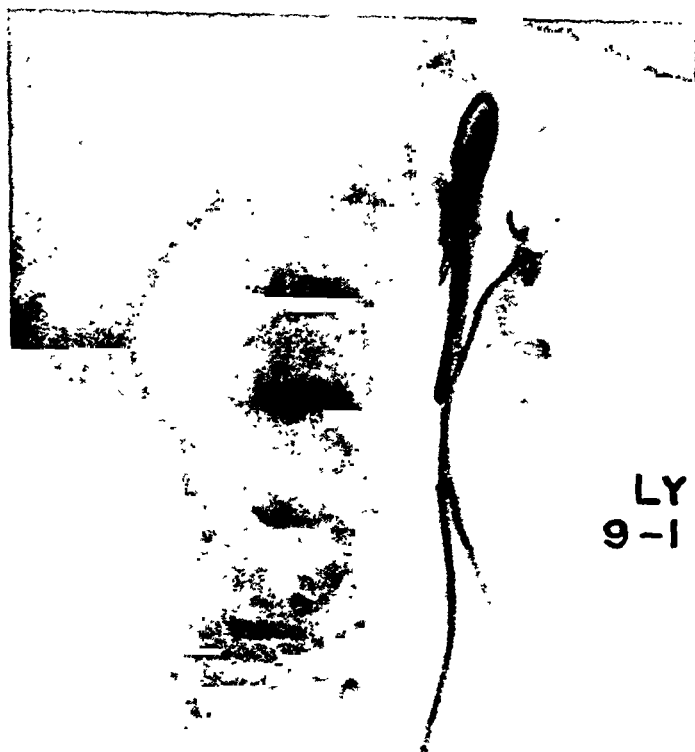


Fig. 4.—Retrograde pyelogram. Double kidney with hydronephrotic atrophy of the upper rudimentary half.



ureterovesical junction is made. As a rule there is no change in the ureteral orifice itself and no obstruction to the passage of the ureteral catheter.

*Unfortunately, the relationship of bladder neck obstruction and the so-called stricture of the ureter is not recognized and these patients are subjected to long courses of ureteral dilatation without obtaining the desired results.* Careful study of these patients has shown that in the majority the primary lesion was not at the ureterovesical junction, but at the neck of the bladder, producing obstruction to urination with hypertrophy of the bladder wall and resulting compression of the ureter in its intramural part. Therefore the treatment should be directed to the obstruction at the bladder neck.

*Bladder Diverticulum.*—Practically all cases of vesical diverticula are congenital and secondary to obstruction at or in front of the bladder neck with the exception of those due to organic disease of the central nervous system. These facts must be borne in mind in the treatment.

There are no symptoms from which a diagnosis can be made and the diverticulum is generally discovered during a routine urologic examination. An intravenous urogram will often disclose vesical diverticula when least suspected. This occurs in both adults and children. Cystoscopic examination often reveals a diverticulum and determines its exact location. However, in the presence of a severe cystitis the opening is easily overlooked.

In 1934, I found nineteen authentic cases of diverticula of the bladder in infants and children in the literature and added two clinical cases and four found at autopsy. The condition is frequently overlooked in children because of the absence of a typical symptom complex. In the six cases reported in my paper, the following symptoms were noted: suprapubic tumor in five; pyuria in three; painful urination, two; chills and fever, vomiting, one; dribbling, one; restlessness, fever, diarrhea, and loss of weight (no urinary symptoms), one; retention, one; difficult urination, one; albuminuria, one; and edema of the left leg, one.

The treatment is directed toward the removal of the obstruction. If the diverticula are small, nothing further than the relief of the obstruction is indicated. However, in large diverticula, especially when they do not empty and infection persists, diverticulectomy is necessary.

*Exstrophy of the Bladder.*—We owe much to the relentless efforts of Coffey, Higgins, Lower, Hinman, Walters, Ladd, and many others who urged early transplantation of the ureters into the bowel. Although Simon first published his technique in 1852 and many authors have described various operations for transplanting the ureters into the intestinal tract, the great stimulus to the treatment of these patients was given by Coffey in 1911. He subsequently modified his original technique and many other authors have presented their various techniques, all of which resulted in a renewed interest in this subject and in the possibility of surgical relief of an intolerable condition.

There is no difference of opinion today on the subject of treatment. Some variances of opinion still exist as to the age when surgery should be undertaken. The general rule was to wait until the child was 3 years of age, so that

control of the bowel function was well established. Higgins in recent years has changed his attitude in that he has seen children of 3 who have already impaired renal function with hydronephrosis and dilatation of the ureters. The determining factor in deciding on operative intervention is the competency of the rectal sphincter in the individual case and before infection has been introduced into the kidneys, and Higgins believes that the operation can be performed any time after the age of 3 months. My preference is to wait until the child is 18 months or 2 years old, and to transplant one ureter at a time. There is increased danger when both ureters are transplanted at once.

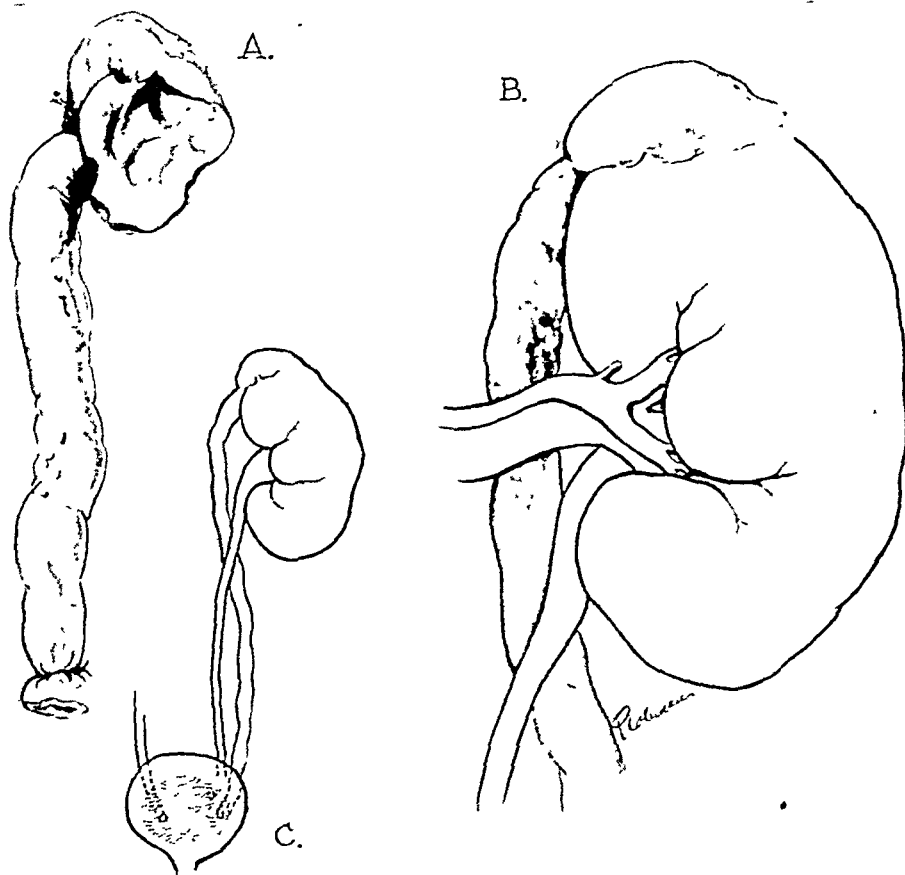


Fig. 5.—A, Marked dilatation of the ureter and hydronephrotic atrophy of rudimentary half; B, crossing of the ureters; C, dotted area illustrates size of uterocoele covering opposite ureter.

*Obstructions at the Vesical Neck.*—With advances being made in diagnostic urology, many abnormalities which heretofore were not diagnosed clinically are now recognized with more frequency. Obstructive lesions at the vesical neck may be of either mechanical or neurologic origin. The causes may be located at the bladder neck or in front of it and may be classified as follows:

(1) contractures at the internal ureteral orifice; (2) median bars; (3) valves in the prostatic urethra; (4) hypertrophy of the verumontanum; (5) lesions of the central nervous system; (6) lesions of the prostate; and (7) extravescical lesions.

Many physicians are still unfamiliar with this pathologic entity and many cases are diagnosed and treated as cases of enuresis.

Of the greatest importance for these children is early diagnosis before irreversible changes occur in the upper urinary tract. The diagnosis of obstruction can be made from the history and the physical examination. The diagnosis of the type of obstruction requires cystoscopic and urethroscopic examination. The use of intravenous urograms and studies of blood chemistry are done in each case.

Our attention should be aroused to the possibility of obstruction by the history of straining, a small weak stream, the fact that it takes the patient a long time to empty the bladder, dribbling during the act of micturition, which may be interrupted once or twice, dribbling between urinations, recurring attacks of infection, and pus in the urine. If, with this group of symptoms, the physical examination shows a suprapubic tumor, the diagnosis of obstruction is complete. There only remains to be determined the cause of the obstruction.

Once the diagnosis has been established the treatment should be carried out immediately.

In 1937, I reported on 101 cases of hydronephrosis in children and found that sixteen were associated with obstruction at or in front of the bladder neck; nine of which were congenital valves, three were stricture of urethra, two were bars, and two were contracted bladder neck. Caulk, in 1936, presented twenty-six cases of urinary obstruction in infants and children which were due to: contractures of the neck in nine; valves in twelve; valve and lobule in one; valve and bar in one; villous mass and valve in one; and lobules in two. Other large series of obstructions at the bladder neck have been reported by Campbell (1937), Mertz and Hamer (1938), Pace (1940 and 1944), and Thompson in 1942.

Contractures of vesical neck may be due to a muscular hypertrophy or a fibrosis of the vesical neck. If urinary difficulty exists from birth, the possibility of a contracted vesical neck should be considered. A complete urologic examination should be carried out and the obstruction removed, either by transurethral resection or suprapubic cystostomy and resection.

The exact incidence of congenital contracture of bladder outlet in childhood is difficult to determine. Many cases are overlooked in childhood until serious symptoms of urinary obstruction appear, and if untreated, the patient dies without the true condition being recognized. Probably this condition occurs more frequently than is apparent, owing to the fact that cases are not reported. Campbell, in 1937, wrote that he had forty-one cases of congenital contracture of bladder outlet in children, and that in a perusal of the literature from 1915 to 1930 he was able to find only twelve cases reported. In 1939, Hendrick-

son and Simon described three cases in children and stated that congenital contracture of the vesical neck is most commonly due to hypertrophy of the musculature of the internal sphincter.

*Extravesical Lesions.*—Grant, in 1938, reported two cases of tumor arising at the sphincteric margin and acting as ball valves. Retroperitoneal lesions, such as tumors, both benign and malignant, occasionally produce urinary symptoms. As the tumor increases in size, it produces obstruction with resulting hydronephrosis. As the tumor continues to increase in size, lateral displacement of one or both ureters results. Lateral displacement of a ureter in the presence of an abdominal mass is almost always pathognomonic of a retroperitoneal tumor. Although these cases are rare, they do occur occasionally, so that one should bear them in mind in any differential diagnostic problem.

*Congenital Valves of the Posterior Urethra.*—Although this interesting pathologic entity was first recognized by the Europeans from studies in the post-mortem room, it remained for the urologists of this country to emphasize the fact that congenital valve obstructions of the posterior urethra were of extreme clinical importance, and diagnosis relatively simple. If not relieved, the effects upon the upper urinary tract are devastating and irreversible.

Valvular obstruction of the posterior urethra is congenital in origin, the embryologic reason being unknown. Langenbeck, in 1802, was the first to give an autopsy description, and subsequent reports that appeared were those of Europeans. Tomatschew, in 1870, was the first to regard congenital valves of the posterior urethra as a definite clinical entity.

Knox and Sprunt, in 1912, were the first Americans to recognize and report a case at autopsy in a child 5 years of age. Autopsy showed bilateral hydronephrosis and hydroureters due to valvular obstruction just below the verumontanum. Hugh Young, in 1912, made the clinical diagnosis of congenital valvular obstruction in the posterior urethra, which was confirmed at autopsy in a boy 17 years of age. In 1913, Young operated successfully through a suprapubic incision in a 20-month-old infant. Young, Frontz, and Baldwin, in 1919, reviewed the Johns Hopkins Hospital records, reported twelve cases, presented an exhaustive review of the literature, and found twenty-four authenticated cases of congenital obstruction of the posterior urethra. In 1920, Young constructed a small "baby punch" which was used on a child of seven with congenital valves of the posterior urethra.

The American literature on this interesting condition has been augmented steadily with further reports which indicate that the condition is not uncommon: Randall (1921); Martinson and Reuben (1923); Randall (1923); Day and Vivian (1923); Hausmann (1924); Beer (1924); Ehrich (1925); Hinman's and Kutzmann's excellent review of the literature in 1925, wherein they reported fifty cases of valvular obstruction in the posterior urethra taken from the literature and to this added six personal cases; Hepler, Poynton, and Sheldon (1927); Kretschmer and Pierson (1929); Young and McKay (1929); Hess and Peters (1932); and Lowsley and Kirwin (1934).

Congenital valves may be destroyed by the fulgurating electrode or the resectoscope. For the relief of bars and contractures, transurethral resection by means of the resectoscope is to be done. Before the development of small punches and resectoscopes, suprapubic operation was the method of choice. Some favored attempts to destroy the valves by using a urethral sound. It is my view that this kind of procedure should give way to transurethral resection.

Unfortunately, the diagnosis is not made early, and although the obstruction has been completely removed, changes in the upper tract are irreversible as illustrated in the following case:

D. O'B., aged 8, male, was admitted to Presbyterian Hospital Nov. 17, 1936. The parents recalled that he has had dribbling of urine since infancy. They agreed with the family physician that this was a behavior and not a medical problem. Three months before his admission to the hospital, pus was found in the urine. He was given a thorough medical regime, but the pyuria persisted. At this time he was sent to another hospital for observation and it was discovered that he did not empty his bladder. Roentgen-ray examination showed enormously dilated ureters, kidney pelves, and calyces. At this time the observation was made that after the patient voided, a large amount of urine could still be expressed by suprapubic pressure. The patient also complained of a slight, dull, aching pain in both lumbar areas.

Physical examination showed the patient to be well nourished and not appearing acutely ill. Head and neck, eyes, ears, nose, throat, heart, and lungs were negative. Examination of the abdomen showed a rounded swelling that extended from the symphysis pubis nearly to the umbilicus.

Examination of the urine: sugar negative; albumin a trace; many pus cells. Cell count showed 4,600 white blood cells per cubic millimeter and the culture showed a pure culture of *Bacillus coli*.

Neurologic examination was negative.

Blood chemistry, November 18, showed urea nitrogen 16.8 mg. per cent; creatinine 1.5 mg. per cent; nonprotein nitrogen 42.1 mg. per cent; phenolsulfonephthalein test appearance time twenty minutes out of two hours 40 per cent.

Cystogram on November 18 showed the bladder outline smooth. There was a reflux into both ureters. Both ureters were markedly dilated, the left being larger than the right. Both kidney pelves were markedly dilated and the calyces were clubbed. The kidney pelves and calyces almost filled the entire kidney.

Cystoscopic examination of November 20 showed the ureteral orifices dilated. There was marked trabeculation of the bladder. The internal urethral orifice was edematous, and there was no median bar. The cystoscope was withdrawn into the prostatic urethra and showed the presence of valves. Following the cystoscopic examination, the patient developed complete retention and 800 c.c. of cloudy urine was withdrawn. The catheter was anchored in place and the patient was treated with an indwelling catheter. Jan. 5, 1937, fulguration of valves by means of Bugbee fulgurating electrode was done. The patient was discharged from the hospital January 10. At this time there were two ounces of residual urine.

The patient was readmitted to Presbyterian Hospital April 8, 1946. He wanted to enlist in the Navy and was turned down because of urinary findings. Examination showed no suprapubic tumor. Urine showed albumin 2+; no sugar; and an occasional red blood cell. Culture showed *Bacillus coli*. Residual urine was 1 oz., blood pressure was 110/70, red blood corpuscles 4,720,000, white blood corpuscles 5,300, and hemoglobin 13.8 Gm.

Cystoscopic examination showed marked trabeculation of the bladder. Both ureteral orifices were wide open. There was marked cystitis; urine was pale.

Retrograde pyelograms showed enormous dilatation of ureters, kidney pelves, and calyces. In spite of the fact that the obstruction was removed, there was no change in the dilatation

of the upper urinary tract. It was assumed that the small amount of residual urine (2 oz.) did not result from the persistence of obstruction but apparently was urine that trickled down into his bladder from his enormously dilated kidney, pelvis, and ureters.

This case illustrates very graphically the need for early diagnosis and treatment in urinary obstruction.

*Hypertrophy of the Verumontanum.*—Obstruction to the outflow of urine may be produced by hypertrophy of the verumontanum, and although it is not as frequent as valvular obstruction, contracture, or bars, it is often undiagnosed, as so many of the cases have been autopsy findings. Usually those cases found were associated with bilateral hydronephrosis and hydroureter. In 1910, Swinburne first called attention to enlargement of the verumontanum as a cause of urinary obstruction. In 1923, Bugbee and Wollstein described a case in a child, 3½ years old; in reviewing the autopsy records of Babies' Hospital they found seven patients with enlarged verumontanum causing obstruction of the prostatic urethra.

*Lesions of the Central Nervous System.*—The common cause of neurogenic bladder disturbance in children is spina bifida, which is usually recognized in the plain roentgen film and should never create any diagnostic problem.

Spinal cord bladder is not a common disease in children. However, the urologist should bear in mind its possibility when the urinary symptoms are prominent and urologic examination does not reveal the cause; then he should suspect some disease process of the central nervous system.

In 1931, I reported three cases in which lesions of the central nervous system produced urinary symptoms. One case was in a female, aged 5½, who had a spinal cord bladder due to poliomyelitis; the second was a malignant tumor of spinal cord with complete retention of urine occurred in a male, 8 years old; and the third was a glioma of the optic chiasm in a girl of 11 years.

*Lesions of the Prostate.*—Among rare instances of urinary obstruction in children is to be mentioned sarcoma of the prostate. McKay, in 1940, reported two cases and Powell, in 1945, in perusing the records of the Montreal General Hospital for thirty-five years, had two cases of sarcoma of the prostate causing vesical neck obstruction.

*Undescended Testicle.*—An undescended testicle is generally discovered during a routine physical examination by the pediatrician. The testis may be found at or above the external ring, in the inguinal canal, or in the abdominal cavity. The condition may be unilateral or bilateral.

Great care must be exercised in making this diagnosis. Patients in whom one or both testes were in the scrotum have been referred to me for operation. During the examination, both testes retracted to the external ring, and the scrotum was empty. It is imperative that one must differentiate between a true undescended testicle and a highly retractile testicle.

The diagnosis of an undescended testicle is made when one or both of the testes remain continuously above the external ring, and when the testes do not enter the scrotum. Many theories are given as to the cause of nondescent of the testes. Embryologists maintain that the descent of the testicle is due to

contraction or atrophy of the gubernaculum testis. However, contradictory evidence has been presented by others. Burdock demonstrated that testicular descent in a normal child occurs before the gubernacular muscle fibers are in evidence. Recently, the causation of cryptorchidism has been attributed to a disturbance of the endocrine glands.

It is to be remembered that many of these undescended testicles do descend spontaneously at or near puberty. Studies have been made which showed that after puberty the undescended testicle does undergo atrophy or remains atrophic. It is claimed by some that the undescended testis is more liable to torsion, trauma, and malignancy. In a large number of cases of undescended testicles there is an associated hernia.

There is still a great deal of difference of opinion in regard to the management of undescended testis. These opinions fall into four groups: (1) that one should wait until puberty before instituting treatment because some of these undescended testes do descend spontaneously at or near puberty; (2) that the patient should be treated with hormones once the diagnosis of undescended testes is made; (3) that the patient should be operated upon just as soon as the diagnosis is made; (4) that the patient should be given a course of hormone treatments and, if the testicles fail to descend, the patient should be operated upon. Those authors holding this opinion believe that the hormone injections make the operation somewhat easier.

One can find sufficient data in the literature to support whatever view he might have on endocrine therapy, despite the various controversial opinions presented.

It should be remembered that there always exists the possibility in the patients who respond to hormone therapy that the testis may have come down without hormones at the time of puberty.

In many patients who have had long courses of hormones, mechanical conditions were the cause for the maldescent—conditions which no amount of hormones could have cured. I believe that true undescended and ectopic testes always require surgical treatment, and do not use hormones before operation. Certainly the hormones have no place in the treatment of retractile testes.

The indiscriminate and long-continued use of hormones is most unfortunate. The stimulating effect of hormones on the growth of the penis and the development of pubic hair in a boy of 10 years or under is most unfortunate. On the other hand, a short course of this treatment for a period of about six weeks, should arouse no objections.

Of interest is the report by Eisenstaedt (1940), who reported marked evidence of degeneration after the use of hormones in a series of patients operated upon. Thompson and Heckel, in 1941, reported successful results in only 27 per cent of their cases. Cone, in 1944, stated, "Our own observations and those of many others have convinced us that artificial stimulation of the retained testis by any gonadotropic or androgenic substances has a small field of usefulness—is practically unnecessary and may be harmful. We must remember that the intimate relationship of the testicle with the thyroid, pituitary, and

adrenal is as yet poorly understood; and it is our belief that stimulation of the endocrine system has harmful potentialities and should be avoided, in that it may result in glandular imbalance or other systemic disturbances." I am in complete accord with the statements of Cone.

#### SURGICAL TUBERCULOSIS OF KIDNEY

Renal tuberculosis in children is of two types: (1) renal involvement as a part of a generalized miliary tuberculosis and, as such with no surgical interest; (2) surgical renal tuberculosis. It is the latter type of lesion that can be cured when the process is limited to one kidney, and when the diagnosis is made early, the prognosis is excellent.

Cases of renal tuberculosis heretofore were rarely observed clinically because (1) localizing symptoms of renal tuberculosis in children are often absent; (2) the general incidence of tuberculosis in this country has been on the decline, which of necessity means less genitourinary tuberculosis; and (3) failure to subject cases of chronic pyuria to modern methods of urologic diagnosis.

With the increased use of diagnostic urologic methods in children, more patients with chronic renal tuberculosis are being recognized and hence are properly treated. With the more frequent use of complete urologic examination in young patients with so-called chronic pyelitis or cystitis, the true incidence of renal tuberculosis will be found to be much higher than the present collected data indicate except in so far as the incidence of general tuberculosis is on the decline.

The consensus of opinion is that surgical renal tuberculosis is comparatively rare in infancy and childhood. Mathe, in 1936, reviewed the various reports given in the literature, including his own personal cases, comprising in all, 4,698 cases of unilateral surgical renal tuberculosis, and found that 565 (12 per cent) occurred in the young from 1 to 20 years. He does not think that renal tuberculosis is rare in children, but that it has often been overlooked in the child.

On the other hand, the rarity of urinary tuberculosis in children is evidenced by the low incidence reported in some series of cases. Hyman, in 1918, presented three cases of renal tuberculosis in children of 10 and 11 years of age and stated that he had seen ten cases of children under 18 with surgical caseocavernous renal tuberculosis. Braasch, in 1920, in reviewing 532 surgical records of the Mayo Clinic on operations for renal tuberculosis from 1894 to 1918, found that two patients fell in the 0 to 10-year group; and 37 cases occurred in the second decade.

Beer, in 1930, wrote that surgical tuberculosis was rare in the young, and in his series of 280 cases of renal tuberculosis there were thirty cases under 20 years of age.

In 1931, I reported eight cases of renal tuberculosis in children up to the age of 14 years, five requiring operation, and in 1936, forty-three cases of renal tuberculosis, fifteen of them occurring before 15 years of age and twenty-eight between 15 and 21.



One must bear in mind the possibility of renal tuberculosis in children who present persistent pyuria and relapsing pyelitis. Careful examination should be made of every case of "chronic" pyuria. However, in the so-called silent renal tuberculosis, no symptoms may appear until the lesion in the parenchyma is far advanced. A perirenal abscess in children, especially one that is followed by a persistent sinus, should always arouse one's suspicions that the underlying cause may be renal tuberculosis. Not infrequently this disease runs a silent course and is discovered during the treatment for other tuberculous lesions. Children have been under treatment for tuberculosis of the bones and joints who had no urinary symptoms but who, during their period of hospitalization, had a persistent pyuria. Repeated studies of the urine showed the presence of the tubercle bacillus. Urologic studies of these children showed rather well-developed, and sometimes far-advanced renal tuberculosis, in spite of the fact that these children never had any urinary symptoms. After establishing the fact that the tuberculosis was unilateral, nephrectomy was carried out. There was no mortality, in spite of the fact that these patients had extensive bone and joint disease.

The diagnosis of renal tuberculosis can be made more readily if the investigation includes a complete physical examination, which may show tuberculous infection existing elsewhere in the body, and repeated studies of the urine show the presence of the tubercle bacillus. The presence of pus and tubercle bacilli calls for cystoscopic examination and ureteral catheterization with careful studies for the presence in one or the other kidney of the tubercle bacillus; smears, cultures, and guinea pig inoculations are carried out as a routine procedure.

Intravenous urography often gives definite information, especially in the well-developed cases. In the early cases a small lesion may be overlooked in the intravenous pyelogram. If the diagnosis of unilateral, renal tuberculosis is made from the urologic examination, one should rarely resort to retrograde pyelography.

Bilateral renal tuberculosis is not amenable to surgical treatment and the prognosis is unfavorable. Once the diagnosis of chronic unilateral renal tuberculosis has been made, provided the opposite kidney is free of tuberculous disease, nephrectomy is the proper course to pursue.

#### URINARY CALCULI

Authors differ in opinion as to the frequency of calculi in the young. The consensus is that urinary calculus is seldom seen in the young in this country, undoubtedly due to better sanitation, improved dietetics, and better care on the part of the pediatrician. In contrast to the foreign literature, which is replete with reports on urinary calculi in children, the literature in this country is comparatively scant, but the condition occurs frequently enough to warrant its serious consideration.

During the nineteenth century urinary calculus was very prevalent among English children and Thompson found in a series of 2,583 cases that one-half

occurred in children under 16 years of age. Rafin, in 1911, reported a series of 322 cases of renal calculi in infancy, of which 139 were found at necropsy. Bokay, in 1912, collected 1,826 cases of urinary stone in children under the age of 15 years. Thompson, in 1921, reported that urinary calculus was found in 25 per cent of the children in China. Noble, in 1931, also found 22 per cent of children under 11 years of age affected in Thailand; Assenfeldt of Austria, found 77 per cent of a series of cases occurring in children.

No such consistently high incidence is found in the American literature. Hill and Stevens in 1920 were able to cite 320 cases of renal calculus, one-half of which were necropsy findings; of these 140 were in children under 1 year of age. In 1922, Thomas and Tanner collected reports from members of the American Urologic Association of 203 cases of urinary lithiasis in the young; of these 112 were discovered with the roentgen ray. Bugbee and Wollstein, in 1924, in 4,903 necropsies found calculi in thirteen infants. Hagar, in 1927, found in a series of 3,295 cases of children under 15 years, bladder stones in eleven of 674; ureteral stones in seven of 813; and kidney stones in fifteen of 1,808. In 1930, Campbell reported thirty cases; seventeen of these were found at autopsy.

In 1931, I reported six cases of urinary calculus in children, and in 1936, published a study of twenty-one children under 13 years of age who had stone in the urinary tract, and concluded that it is a relatively uncommon disease in this country.

Tudor, in 1943, found that seven patients among 10,650 children admitted to the Duke Hospital had vesical stones, and stated that in America less than 2 per cent of the afflicted persons are children.

The cause of primary urinary calculus is unknown. Many theories have been presented as to the etiology of stone such as familial and racial influences, geographical locations, diet, and metabolic disturbances. Family history is of great importance in one type of calculus, namely, in the patient with cystine stone, since it is well known that in this type of stone, other members of the family may have cystine stones or cystinuria. In 1916, I reported two cases in twin brothers of cystinuria complicated by cystine stones in the bladder, and in 1930, three patients, one of which was in a male aged 12. Many members of the families of these cases showed the presence of cystine in the urine.

In the very young, the symptoms of stone are abdominal pain, vomiting, diarrhea, convulsions. As the gastrointestinal symptoms are very prominent, the presence of urinary calculi is not suspected, and they are found only on routine x-ray examination.

Pyuria is the major symptom of urinary stone in children. This has been stressed by Hyman (1926), who found it to be present in 30 to 50 per cent of his cases, and Thomas and Tanner (1922) in 31 per cent. Mertz and Lewis in 1934 reported pyuria in nine out of ten cases.

If there is hematuria accompanied by recurrent colicky pain, a stone should be suspected. Disturbances of micturition are frequency of urination, dysuria, and dribbling. Several children were admitted to the hospital with the diagnosis of acute appendicitis. The finding of fresh red blood cells in the urine led

to roentgen-ray examination with the resulting diagnosis of kidney or ureteral stones. In several patients the clew to the true pathology was the finding of cystine crystals in the urine.

Several patients with stone in the bladder with great frequency and dribbling were treated for a long time as cases of enuresis, without relief of symptoms.

Diagnosis in the child is the same as in the adult. Urinalysis, x-ray, intravenous pyelography, and cystoscopy should all be utilized.

The pathologic changes associated with the urinary calculus are the same in the child as in the adult. Stone may be accompanied by (1) hydronephrosis, (2) pyelonephritis, (3) pyonephrosis, or (4) perinephritic abscess.

Stones in the kidney that are obviously too large to pass, or that have produced hydronephrosis, stones that produce recurring attacks of chills and fever, hematuria, or that produce a chronic pyuria, should be operated upon.

It is possible to remove the stones by means of pyelotomy. This is easier than nephrotomy, less dangerous, carries with it a much lower operative mortality, and there is no danger of secondary hemorrhage, such as occurs with a nephrotomy.

Small stones in the ureter that show a tendency to progress down the ureter with each attack of renal colic, in cases where there is little or no infection, can be carried along with fluids and diuretics. If the urine shows cystine crystals, soda bicarbonate should be given. On the other hand, where the stones are obviously too large to pass and where a marked hydronephrosis exists, extraperitoneal ureterotomy is the operation of choice.

Small stones in the bladder can be treated with litholapaxy in a number of patients.

I would like to stress at this time the importance of clearing up residual infection after removal of the stone by surgical measures.

#### HYDRONEPHROSIS

Before the era of modern pediatric urology, most of the cases of hydronephrosis and hydroureter were not recognized, and the early literature deals with cases found at autopsy. The writings and investigations of Eisendrath, Henline, Hinman, Hyman, Kretschmer, Priestley, and many others have broadened our knowledge on this subject. As in other urologic diseases, it is imperative that early diagnosis be made so that early treatment can be instituted, if irreparable damage to the kidney is to be prevented.

There is no typical symptom-complex of hydronephrosis, and many times the disease runs a silent course. In some cases of indefinite and obscure abdominal pain, the presence of hydronephrosis is found during routine urologic examination. As a rule, most of these cases come to the attention of the physician after the onset of infection. When infection supervenes, patients have chills and fever, frequency of urination, and pyuria. Because of the presence of pyuria with chills and fever, many of these cases are erroneously diagnosed as acute pyelitis or acute cystitis.

Hydronephrosis due to adhesions in children is rare but does occur (Fig. 6).

Any patient suffering from recurring attacks of pyuria or in whom the pyuria does not respond to the usual medical management should be subjected to a complete urologic study. When the hydronephrosis is large, a palpable swelling in the renal area is often present at the first examination. When bilateral hydronephrosis is present, the condition may be confused with Wilms' tumor.

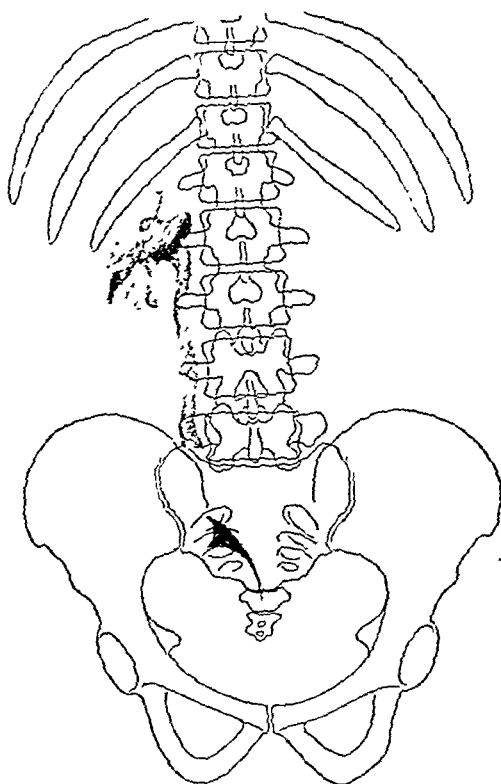


Fig. 6.

Fig. 6.—Hydronephrosis due to a dense, fibrous band at the sacral level.

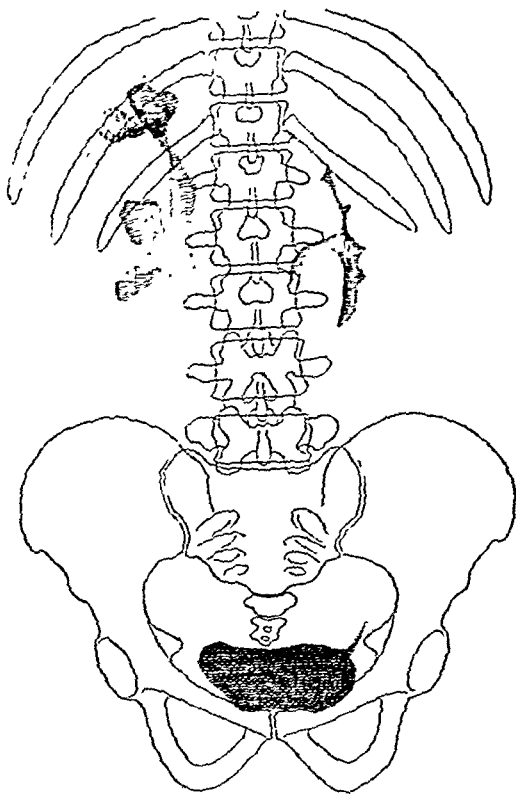


Fig. 7.

Fig. 7.—Hydronephrosis in a double kidney with severe infection resulting in death of the patient.

Hydronephrosis and hydroureter may result from the following:

1. Obstructions in the lower urinary tract anywhere along the course of the urethra from the external meatus to and including the vesical neck. The most common obstructions of the posterior urethra and vesical neck are contracted vesical neck, posterior urethral valves, cysts and hypertrophy of the verumontanum, strictures of the urethra, and median bars. In 1937 I found sixteen in 101 cases of hydronephrosis associated with bladder neck obstructions, nine of which were due to congenital valves, three due to stricture of urethra, two to median bar, and two to contracted bladder neck.

2. Obstruction at the ureterovesical junction. Narrowing or obliteration of the ureter is one of the frequent causes of hydronephrosis and hydroureters. Cases have been reported by Buerger (1914), Kakels (1918), Wason (1920), Mixter (1922), Hahn (1924), Campbell (1933), and Hinman (1929). In 1933, I became interested in determining whether or not hydronephrosis was due to stricture of the vesical end of the ureter in the generally accepted interpretation of that word, and reported on fifteen cases. Stricture was present in only three patients, all of whom had an anomalous insertion of the ureter and the twelve remaining patients showed that hypertrophy of the muscular coat of the ureter was the cause of the obstruction.

Obstruction to the flow of urine at the ureterovesical junction may also be due to ureterocele or cystic dilatation of the ureter, of which I have seen six examples, one of which has been previously mentioned in this paper.

Bray, in 1939, reported two cases: in one there was a hypoplastic right kidney and hydronephrosis of the left kidney with strictures at the ureteropelvic and ureterovesical junctions; in the second there was bilateral congenital stricture of the ureteropelvic junction. Henline and Menning, in 1943, reported four children in whom the hydronephrosis was caused by ureteropelvic obstruction due to intrinsic stenosis. They stress the fact that many times several factors are present in causing an obstruction of the ureteropelvic junction and that it is important that the primary cause be corrected, as too frequently only the secondary factor is taken care of.

3. Obstruction at the ureteropelvic junction is not uncommon and may be due to either aberrant blood vessels, fibrous adhesions around the ureteropelvic junction and strictures at the ureteropelvic junction, or, occasionally, stone in the ureteropelvic junction.

Since Boogaard's description (1857) of the kinking of the ureter around an anomalous vessel, no unanimity of opinion prevails as to the role played by the aberrant renal vessel in hydronephrosis. Some authors believe hydronephrosis results from direct compression of the ureter by the vessels; others are of the opinion that there is some renal ptosis which in turn causes the aberrant vessel to compress the ureter; and there are those who think that there must exist a combination of factors, consisting of a movable kidney plus a fixed point caused by a vessel or band in the ureter either at, or in close proximity to, the ureteropelvic junction. There are some who believe that the hydronephrosis is not caused by the aberrant vessel and the presence of a hydronephrosis should not be ascribed to the presence of an aberrant artery.

The finding of anomalous renal vessels causing upper urinary obstruction is not frequent in children. Cases have been reported by Campbell (1933), Jewett (1939), Fite (1940), White and Wyatt (1942), and Moore (1942).

4. Pathologic conditions extrinsic to the urinary tract, i.e., pressure on the ureter from without. This is rarely found in children and is generally associated with retroperitoneal tumors such as large sarcomas and lipomas (Fig. 8). A recent case reported by Kereszturi in 1940 was that of an imperforate hymen which caused hydrocolpos in early infancy, and this in turn, through pressure

on the urinary tract, led to bilateral hydronephrosis and hydronephrosis, pyuria, and bacilluria. Retroperitoneal tumors may cause marked displacement of the kidney and ureter without hydronephrosis (Figs. 9 and 10).

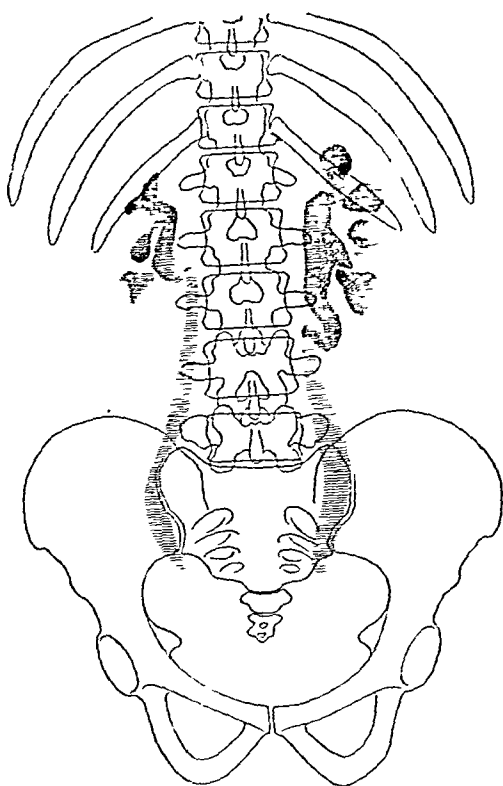


Fig. 8.

Fig. 8.—Bilateral hydronephrosis with lateral displacement of the ureters due to a retroperitoneal tumor.

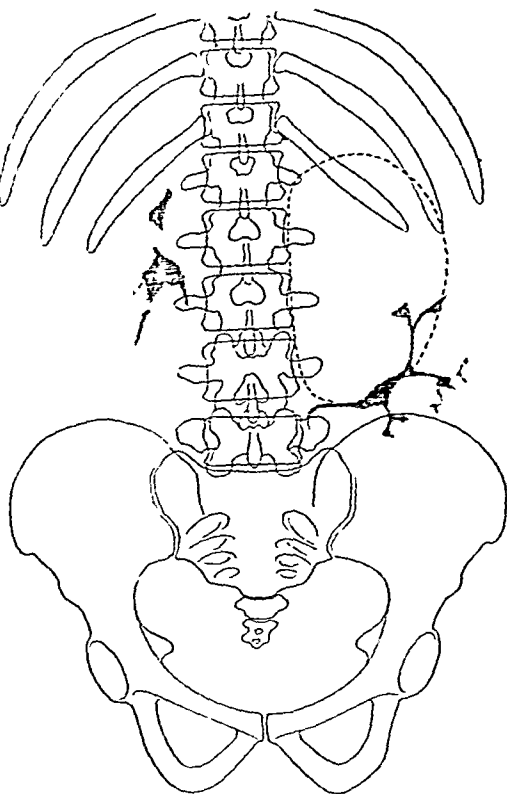


Fig. 9.

Fig. 9.—Marked displacement of the kidney by a retroperitoneal tumor without hydronephrosis.

5. Hydronephrosis due to lesions of the central nervous system, such as one sees in spina bifida in children, where enormous hydronephrosis develops, and the nervous influence in adults, such as tabes dorsalis and spinal cord changes in pernicious anemia. These cases of hydronephrosis are explained on the basis of neuromuscular dysfunction without an anatomic explanation for its development. The hydronephrosis may be unilateral or bilateral. Generally, it is bilateral.

*Treatment.*—Treatment naturally depends on the cause of the condition. Obstructions in the lower urinary tract are removed by appropriate surgical measures as discussed previously in this paper in the section on obstructions of the lower urinary tract.

Strictures at the ureterovesical junction respond well to ureteral dilatation. The treatment of obstructions at the ureteropelvic junction depends on the

cause of the obstruction and generally requires surgical intervention. In some cases ureteral dilatation may be tried.

Stones naturally must be removed, preferably through a pyelotomy incision. Aberrant blood vessels may be divided. So-called strictures may be treated by surgical methods in which the various plastic operations are employed. Recently, there has been a tendency to employ the Rammstedt type of operation.

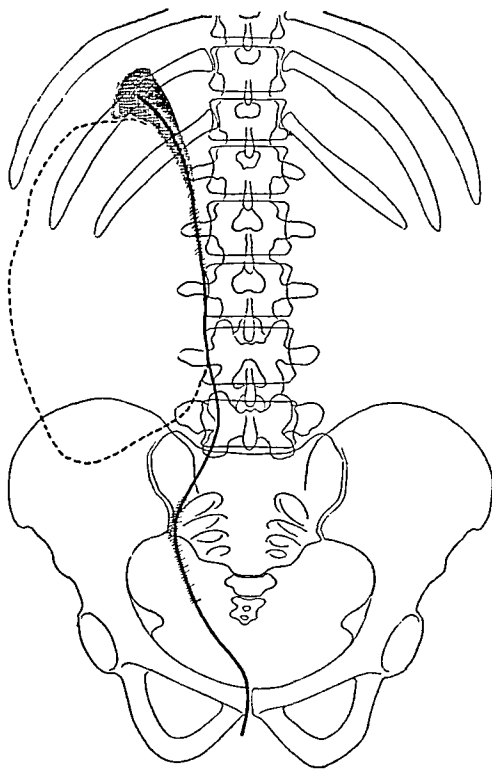


Fig. 10.—Upward displacement of kidney by a retroperitoneal tumor without hydronephrosis.

#### TUMORS OF THE URINARY TRACT

Tumors of the genitourinary tract in infancy and childhood, with the exception of kidney neoplasms, are rare.

*Bladder Tumors.*—Most of the literature dealing with bladder tumors concerns reports of a single case, together with an extensive review of the literature. The common bladder tumor in infancy and children is the sarcoma.

Excellent reviews on bladder tumors in the young have appeared since O'Neill's résumé in 1915 and Deming's report in 1924 of sixty-four authentic cases occurring in the first decade of life, including two of his own. Beer, in 1930, observed no bladder tumors in children in 500 personal cases. Rathbun, in 1937, covered seventy-five cases from the literature and reported a personal observation of hemangioma of the bladder in a 27-month-old baby. Segal and

Rink, in 1942, covered the literature on cavernous hemangioma of the bladder since 1869 and found forty-one cases, fourteen patients being under 20 years of age. They added to this figure their own case in a boy 15 years old.

Mertz and Hamer, in 1938, reporting on 167 patients, had two cases of bladder tumors in children, one a sarcoma and the other a chloroma. Campbell has seen three cases of bladder tumors in the young and another case where a sarcomatous nodule in the bladder was part of a generalized metastasis.

Dean, in 1940, remarked on the rarity of vesical tumors in childhood. From his study of published reports and records of the Memorial Hospital for Cancer and Allied Diseases in New York he found an approximate incidence of one bladder tumor in a child to each 950 bladder tumors in adults, mainly sarcomas.

Chalkley and Bruce, in 1942, reported a neurofibromatosis of the bladder in a 9-year-old boy, and found only one other case recorded (by Kass) occurring in a child.

Crane and Tremblay, in 1943, published an exhaustive survey since 1905 on sarcoma of the bladder and found thirty cases reported in children from one to nine years, and nine cases from 10 to 19 years of age.

I have seen only one tumor of the bladder in a child. This was an angioma of the bladder. The tumor was destroyed through the cystoscope with the high frequency current. My experience on the rarity of bladder tumors in children coincides with the experiences of other urologists.

Hematuria is the most frequent symptom of vesical tumor in children. When the disease is well advanced, interference with urination, which may result in an overdistended bladder, takes place. Many of these tumors develop "silently." On occasion, the tumor has been discovered in female infants only when it protrudes from the urethral meatus. The diagnosis is made by cystoscopic examination. Unfortunately, when these patients are presented for examination, the tumor has progressed so that the general health of the child is poor and the possibility of surgery affecting a cure is exceedingly remote. However, because clinical experience with irradiation is meager, little information is available regarding the radiosensitivity of these tumors.

It is to be hoped that, if we bear the possibility in mind that children with hematuria might have a tumor of the bladder, the patients will be given the benefit of a cystoscopic examination and these tumors will be recognized early, i.e., when they are small, so that the children can have the benefit of radical surgery.

*Tumors of the Kidney.*—It is only recently that the subject of renal tumors has received a good deal of attention.

Before the advent of pediatric urology, kidney tumors in children received scant attention. The nomenclature was confusing, the diagnosis was generally made late, and the operative mortality was very high. As a result of modern urologic diagnostic methods, the urologist, and then the pediatrician, became greatly interested. As more and more of these patients were operated upon,



the interest of the clinician and the pathologist in the pathology of these tumors was awakened, and finally the roentgenologist was drawn into the picture, not only in the interpretation of the pyelograms, but in therapy as well.

No longer are indefinite and confusing terms used to describe this entity, but instead it has been definitely established that these tumors are almost always of the type first described by Wilms and are now called Wilms' tumors.

Wilms' tumors are the most common malignant tumor of the genitourinary tract in children. The great proclivity of infants and children to malignant tumors of the kidney and the eye is in marked contrast to the rarity of these tumors in the adult. These tumors occur in the very young, although cases have been reported in the adult. Because of this fact, it is universally agreed that they are congenital in origin. There is, on the other hand, no agreement concerning the genesis of Wilms' tumors, and many theories have been advanced, among them being: (1) origin from aberrant germ plasm of the primordial segments; (2) origin from the wolffian body (this theory has such adherents as Ebert, Doederlein, and Birch-Hirschfeld; Dean and Pack have never been able to ascertain any wolffian remnants in the human kidney, and discard this theory as untenable); (3) origin from renal blastema or nephrotome, which theory Wilms upheld; (4) origin from endothelial cells, which embraces theory of metaplasia to explain the variegated microscopic picture (advanced by Brosin in 1884). Dean and Pack believe that these embryonal renal adenomas originate at different developmental periods of the embryo, the renal blastema or nephrotome being the predominant contributing structure. Geschickter and Widenhorn (1934) state that the earlier theories of pathogenesis relating Wilms' tumor to the wolffian body or to aberrant rests from the seletrotome or myotome have been superseded by data relating these tumors to embryonic nephrogenic tissue (the relationship first set forth by Muus). Weisel, Dockerty, and Priestley of Mayo Clinic, from the various theories presented, came to the thought that mixed renal neoplasms possibly originate (a) from embryonic cellular rests; (b) from one or more germ layers (teratomatous); or (c) from the mesenchyma of the embryonic kidney, through a process of perverted growth and metaplasia.

Dean and Pack, in 1932, studied 19,129 cases of neoplastic diseases at the Memorial Hospital for Cancer and Allied Diseases from January, 1917 to January, 1929, inclusive. Of these 16,565 were malignant, and the sixteen embryonal adenomas of the kidney reported in this study constituted 0.083 per cent of all admissions and 0.096 per cent of all malignant tumors treated during this period. Later in 1940, Dean stated that twenty-four cases of Wilms' tumor of kidney were seen so far at the Memorial Hospital. Other reported cases of Wilms' tumor in children are those by Campbell (1937), Mertz and Hamer (1938), and Weisel and associates (1940).

Of the three constant symptoms of renal tumors in general, namely, a visible or palpable tumor, hematuria, and pain, only the first is constant in malignant renal tumors of children. The abdomen swells gradually, becoming

asymmetrically or symmetrically global. Fever is next in constancy and may be intermittent, remittent, moderate, or high.

In contrast to the hypernephroma, the Wilms' tumor seldom causes hematuria. In the adult, hematuria is the common symptom of renal tumor. In children hematuria is rare. I have only seen one case of Wilms' tumor in a child in whom a history of hematuria was obtainable. Hematuria, when present, is usually due to hemorrhage from the parenchyma of the congested kidney rather than from the tumor itself.

Unfortunately, the common condition which brought the patients to me was the presence of an abdominal tumor, often found by the mother or nursemaid, generally when the tumor had reached an enormous size. In contrast, it is to be stated that many have been recognized by the pediatrician during a routine physical examination.

The absence of pain also tends to prevent its early discovery. Pain, when present, is of the colicky type. Pressure symptoms appear in accordance with the growth of the tumor, e.g., cough, dyspnea, ascites, edema, constipation. Vague gastrointestinal symptoms bring the child to the doctor, who, on palpation, finds a good-sized abdominal mass. In an early stage, tumors on the right may simulate appendicitis. As pain is absent early in the course of the disease, there is nothing to direct attention to the kidney. In two series of cases, a total of twenty-four patients, reported previously by me, the one common symptom was palpable tumor, which was present in every instance. Fever was present in eleven instances, abdominal pain in eight, loss of appetite in seven, loss of weight in six, vomiting in four, frequency in two, burning in one, and hematuria in one.

Differential diagnosis concerns excluding other renal lesions, of which hydronephrosis is the commonest, and other retroperitoneal lesions, such as sarcoma and lipoma, which can be excluded rather easily. In other retroperitoneal tumors, the course of the ureter as shown with the shadowgraph catheter is quite typical. In these cases there is a lateral displacement of the ureter.

Diagnosis should be based on the presence of a palpable tumor and changes in the urogram. Excretory urograms will show deformity of the pelvis and calyces. Ureteral catheterization is to be carried out to determine the functional capacity of the kidney. A plain roentgenogram of the chest is indicated in each case to rule out the possibility of metastasis, and a plain film of the abdomen will rule out stone in the urinary tract. It is the consensus of opinion that under no circumstances should one incise a Wilms' tumor for biopsy, as this destroys the capsule of the tumor and encourages more rapid and widespread growth. Also, frequent palpation of the tumor is inadvisable as metastases from Wilms' tumor are generally blood borne. Once the diagnosis is made, there should be no more palpation.

An interesting phenomenon occurs in the changes in the pyelograms made at the end of the preoperative radiation. This phenomenon was described by me in a previous publication. In the cases that respond to radiation, that is,

in which the tumor shows marked regression in size, the pyelogram has a normal or a nearly normal configuration.

There are still some differences of opinion regarding treatment, and these fall into three groups:

1. Those who believe in roentgen therapy alone. They are in the minority and some of them now advocate surgery if there is a cessation in the diminution of the size of the tumor. It is to be remembered that after the tumor has diminished in size following radiation therapy, should it then begin to increase in size, the tumor is no longer sensitive to radiation.

2. By far the largest number of urologists believe in a combination of deep therapy and nephrectomy. A course of deep therapy is given before operation. Although not all Wilms' tumors do respond, the majority show a rapid diminution in size. When the tumor no longer diminishes in size under roentgen treatment, having become stationary, nephrectomy is carried out at once, and this is followed with a course of postoperative radiation. This technique has resulted in a great reduction of the operative mortality, which today is practically nil, since the diminution in size of the tumor makes nephrectomy a simple procedure.

3. The third group perform nephrectomy as soon as the diagnosis is made. Ladd and White believe that the chance of survival for a patient with embryoma of the kidney is far greater if the policy of immediate operation is adopted rather than the policy of delayed operation following roentgen therapy.

It seems wise to issue a word of caution in the study of these cases. Once the diagnosis has been made, I do not believe that these tumors should be subjected to repeated palpation by the house staff and the students, since repeated and often severe manipulation may be a factor in the dissemination of tumor cells and hence a factor in metastasis.

#### SUMMARY

1. Age is no longer a contraindication to complete urologic examination in infants and children.

2. The persistence of pus in the urine demands complete urologic examination.

3. Relapsing or recurring attacks of cystitis and pyelitis demands complete urologic examination.

4. Lesions of the urinary tract in children are the same as in adults.

5. Certain lesions are seen more frequently in children than in adults, namely, Wilms' tumors.

6. Lesions of the bladder and prostate common in the adult are uncommon in children.

7. The splendid early cooperation between pediatrician and urologist has resulted in a shortened period of morbidity and in preventing destruction of vital organs.

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# The Academy Study of Child Health Services

## THE HISTORICAL BACKGROUND OF THE STUDY OF CHILD HEALTH SERVICES

In 1931, when the American Academy of Pediatrics was organized, there was a vast store of new knowledge in all fields of medicine. New skills and new techniques had been developed for the cure and prevention of disease. But the means of bringing these newly acquired medical skills to those who needed them had advanced little, if at all. For the most part, it was the wealthy and the very poor who benefited from the new advances in medical knowledge; the masses of people in between were left out of the new horizons in medical knowledge except at a crippling cost to themselves and their families. The immediate problem, therefore, which faced the medical profession at the time of the founding of the Academy was essentially a problem in the distribution of medical care.

How to make quality medicine available to all mothers and children regardless of wealth, race, or creed was a question of primary concern of the Academy at the time of its organization and has, either consciously or unconsciously, remained the chief preoccupation of the Academy during the fifteen years of its existence. The answers to this problem of distribution are not simple. In all times the more equitable distribution of wealth, of the products of the hands, of the benefits of science and of the quality care of the sick have been sought and not found. That failure presents no reason why the answers should not be continually sought.

That the Academy was seeking new answers is amply borne out in the first report of the Committee on Hospitals and Dispensaries. In June, 1931, Dr. Gerstenberger, Chairman of the Committee, recommended that the "Academy set about securing regularly accurate information as to the existing facilities and needs of hospitals in the United States and Canada caring for infants and children; of independent institutions and independent pediatric departments of general hospitals and of wards for infants and children existing as units or parts of medical services. This survey is to include medical, nursing, dietetic, social and administrative services." As this proposed survey covered between 6,500 and 7,000 hospitals having a certain relation to children, it led Dr. Grulee to remark that "Dr. Gerstenberger had bitten off a pretty large bite."

This report of the Committee on Hospitals and Dispensaries was sympathetically discussed and was then laid aside rather wistfully as being impractical at the moment. It is, however, notable in that it accurately foreshadowed an action which was to be taken by the Academy a dozen years later. Moreover, it outlined in some detail the lines of the study in which the Academy is at the moment engaged. All will agree that in 1931 the survey was not a practical project for the Academy to undertake. It was something like entering a newborn babe in an intercollegiate race. In view of the immaturity of the infant Academy, failure would have been a certainty, but it was proper to fix a goal, even that early, with the hope and expectation that the day would arrive when a winning race could be run.

The germ of the idea of a study of child health services appeared also in Dr. Isaac Abt's address which inaugurated the Academy in 1931. He stated that "The prime object of medical organization is the dissemination of medical knowledge." He urged that the educational qualifications of pediatricians be studied and that the improvement of the general standing of hospitals, the study of the nursing and social services, and the interest of the Academy in undergraduate and postgraduate instruction in pediatrics be fostered. He emphasized the importance of Dr. Grulee's report, which demanded that the Academy study the status of the general hospital and dispensary for sick children, the need of health clinics,



the desirability of a positive stand for the development of preventive measures against disease and infection, and many other points and objectives which the present Committee for the Study of Child Health Services has on its agenda of study.

Like a scarlet thread running through a bolt of cloth, the idea keeps reappearing in the discussions of the Executive Board and in committee reports. Like the "old man of the sea" the idea would not down until finally it became plain that if the Academy of Pediatrics were to fulfill its destiny, it had to undertake a survey of child health services throughout the nation. That 1944 was to be the year of decision was inherent in all its acts from the moment of birth. The Study of Child Health Services was no accident, nor was it the consequence of a sudden burst of energy. The twelve intervening years were the years of preparation to take on a task that had by its magnitude daunted every other medical group interested in the welfare of mothers and children.

As early as 1935, the Academy Committee on Child Health Relations urged that Academy groups undertake to inform themselves on the status of child health activities in their state, the provision for medical care and health supervision of children in institutions or under the care of agencies, both official and voluntary, the medical and health needs of children in their states, and the basic facts of mortality and morbidity among children in their state. The purpose of the resolution was "to appraise the work already done and to improve the health and medical care of children through cooperation" with all possible agencies.

The Committee on Medical Legislation, which was formed in 1935, has from the first been an active committee reporting on and analyzing all federal health bills introduced in Congress having to do with the medical profession. The Academy owes this Committee a deep debt of gratitude for the education given its members. The reports of 1936, 1939, 1943, and 1946 were all notable in forming the policies of the Academy. Again and again by direct statement and by implication, the point is stressed that the facts on which a wise and comprehensive health plan can be based are not known to the medical profession nor to any agency either public or private.

Dr. Wall's report to the Executive Board in June, 1944, on the EMIC program and the resulting recommendation that the special committee on the EMIC's program "include in its studies the question of facilities available for the health supervision of infants and for promoting the welfare of children" brought to a head a gathering storm of protest directed against the Children's Bureau. At about this time, attention was called to the fact that the functions of the Children's Bureau had been abruptly changed so that in 1944, it was an active factor in the practice of medicine throughout the United States, regulating fees and conditions of practice on a federal scale. It was at this June meeting of 1944 that the Academy nearly broke off relations with the Children's Bureau. This controversy called forth a letter from Dr. Grover Powers in defense of the Children's Bureau and caused Dr. Borden Veeder and Dr. Lee Forrest Hill to write an editorial in the December issue of the *JOURNAL OF PEDIATRICS* (1944) stating the position of the Academy not only in the matter of the EMIC's program, but also advocating a Federal Bureau of Health and foreshadowing the Study of Child Health Services.

The differences with the Children's Bureau and the proposed health bills in Congress were all to the good in so far as they made physicians not only take a stand, but, of what was of more importance, to think problems through. It was no longer enough to do a passable routine job, for it was necessary for physicians to orient into the general social scheme their ancient function of curing disease. The public was not only demanding care of high quality at the bedside but also they had a well-grounded suspicion that prevention of illness was even a better objective.

It is thus very clear that the Study of Child Health Services is no accident. Rather, it is an inevitable product of the Academy's development, waiting only on the Academy's growth to maturity and the logical timing of the effort. During its brief history, the Academy has been in agreement with the common longing for better maternal and child health programs

for all the people, but has been firm in its demand that hasty and poorly-conceived legislation be strictly avoided. An honest bill aimed at the improvement of medical care cannot be written until the facts are known. Any such bill should be based upon knowledge of what we have, what we lack, and what we need.

With the year 1944, the twelve years of preparation were ended and the Academy was ready to set out on the task of finding the facts, facts which should speak for themselves and write their own program of good health for all mothers and children.

MARSHALL C. PEASE, M.D., Historian

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## Academy News and Notes

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The following members have been released from service:

Thomas A. Gibson, Winchester, Va.	(Army)
David W. Goltman, Memphis, Tenn.	(Army)
Harold Jacobziner, New York, N. Y.	(Navy)
H. A. Slesinger, Windber, Pa.	(Army)
Joseph McBride Sloan, Corpus Christie, Texas	(Navy)
Frederick F. Tisdall, Toronto, Ont.	(R.C.A.F.)
E. V. Turner, Columbus, Ohio	(Navy)
Raeburn James Wharton, Johnson City, N. Y.	(Army)

# The Social Aspects of Medicine

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Dear Dr. Park:

At the American Academy of Pediatrics Legislation Committee luncheon in Pittsburgh on February 25, it was suggested that the committee present a statement of basic principles that should govern our consideration of medical care plans.

In this connection it was pointed out that a committee of the Massachusetts Medical Society representing all shades of thought in the society was able to reach a unanimous conclusion concerning such basic principles.

I am enclosing a copy of these basic principles adopted by the Massachusetts Medical Society, together with a practical application of these principles in an actual review of the Wagner-Murray-Dingell Bill and the Maternity and Child Health Act of 1945.

It was suggested that the members of the American Academy of Pediatrics might be interested in having these principles made available to them through your department in the JOURNAL.

Sincerely yours,

(Signed) STEWART H. CLIFFORD, M.D.

## BASIC PRINCIPLES ADOPTED BY THE MASSACHUSETTE MEDICAL SOCIETY WHICH SHOULD GOVERN MEDICAL-CARE PLANS

The objective of adequate medical care in our free society is to make available to everyone—regardless of race, color, creed, financial status or place of residence—every known essential preventive, diagnostic and curative medical service of high quality. The attainment of such medical care must necessarily be an evolutionary process which will require the co-operation of all concerned over a period of years.

The success of any plan for medical care is dependent on the mutual co operation of the public, those rendering professional services and the administrative agencies. This co-operation can be obtained only if those rendering the services are convinced that they will have a continuing authoritative voice in the formulation and execution of policies and plans, thereby assuming their proper share of responsibility.

Provision of adequate medical care for those unable to obtain it by voluntary prepayment plans or by direct payment is the responsibility of the local or state government. Part of the burden of this responsibility may be assumed by charitable agencies. Federal grant-in-aid to state programs administered by state boards of health is an acceptable method of helping to meet this responsibility.

The medical care of those who are able to purchase it by voluntary prepayment plans or by direct payment is the responsibility of the individual.

Eligibility for receiving benefits under a program aided by federal grants should be determined by the individual states.

The patient shall have free choice of his physician, group of physicians, clinic or hospital from among those participating in any plan, provided that the physician, group of physicians, clinic or hospital shall have the right to refuse or to accept the patient.

Physicians and other qualified persons rendering medical care shall receive adequate remuneration for their services.

The physician shall be free to elect or reject without prejudice participation in a medical care plan. The rights of the physician as to the choice of methods by which he is to be paid shall be fully protected.

The Massachusetts Medical Society looks upon these basic principles as essential to the development of any successful medical care plan and, as guides by which to evaluate medical care plans that may be proposed in the future, with the understanding that changing conditions may require their later revision.

THE SOCIETY LOOKS AT  
THE WAGNER-MURRAY-DINGELL BILL (SENATE 1606) AND  
THE MATERNITY AND CHILD WELFARE ACT OF 1945 (SENATE 1318)

Senators Wagner and Murray introduced the National Health Act of 1945—Senate 1606—in the United States Senate on November 19, 1945, the day on which the President's message dealing with this subject was read to the Congress.

The interest of the Massachusetts Medical Society is largely centered in titles one and two of the act.

Title one authorizes grants-in-aid to states to extend the public health services, to increase maternal and child health services and to provide medical care for the needy.

Title two makes provisions for full medical, dental, nursing and laboratory care and hospitalization for those able to pay for such services.

The Massachusetts Medical Society with regard to title one, part A, cites the progressive leadership that the physicians of New England have always shown in the development of public health enterprises, and its adoption as a principle the making available to everyone, every known essential, preventive, diagnostic and curative medical service of high quality. We do approve in general this part of the bill as written, with the following exceptions:

The responsibility for the training of personnel should be the duty of the states and not that of the federal government, as designated in section 314A.

Provision should be made which would ensure proper representation of the professional organizations on the advisory council—section 314F.

Responsible private agencies, such as the Blue Cross and the Blue Shield, should be included among those with whom the state health agency may make working agreements—section 314H.

The state administrative agency should be required to consult with professional advisory committees before issuing regulations, which in turn should be issued only after due notice—section 314H.

The Society believes that the objective of title one, part B is more clearly covered in Senate Bill 1318.

With respect to title one, part C, the Society approves of federal grant to aid the several states in assuming their responsibility of providing medical care for those unable to pay for such services. It approves, in general, of this part of the bill as written with the following exceptions:

Federal grants-in-aid for the medical care of needy persons should be made by the United States Public Health Service to state departments of public health.

It disapproves of the provision that places the responsibility in the Social Security Board on the federal level and in the department of welfare on a state level—section 131.

The Society through its Blue Shield having approved of the service principle rather than the payment to patients of cash benefits for medical care, disapproves of the provision in the bill which makes cash payments to individuals for this purpose.

Title two is compulsory health insurance. It would be very costly to carry out the provision of this section of the bill, and there is nothing to intimate what this will add to the burden of the taxpayer or how the money will be raised. Since the Society believes that the payment for medical care of those able to pay for such services by direct payment or on a prepayment basis is the responsibility of the individual and that with the extension and development of voluntary or other plans particularly adapted to certain areas, medical care of the highest quality can be obtained at a reasonable cost, it disapproves of this section.

The Maternal and Child Welfare Act of 1945—Senate 1318—is designated as an act "to provide for the general welfare by enabling the several states to make adequate provision for the health and welfare of mothers and children and for services to crippled children."

The Society finds serious objections to this bill as written. Some of the more important of these are as follows:

The bill makes no adequate provision for general public health programs that are more fundamental than this specialized legislation.

Services and facilities are available to all who elect to participate, regardless of economic status. (This violates Basic Principles 4 and 5.)

The public deserves a reasonable estimate concerning the ultimate cost of this proposed legislation. Experience and such factual data as are available indicate an ultimate annual budget approximating one billion dollars. This should be clearly recognized in any consideration of the bill.

Fee-for-service method of payment is restricted to consultation or emergency visits and is not ordinarily available to practitioners or specialists.

The bill does not make clear just who is to decide the fee for a given service that would be considered adequate remuneration in an individual state, nor does it make provision for variable fees to meet the differing costs in the several states.

The bill does not prohibit professional personnel, groups or institutions rendering service under the program from accepting supplemental payment from or on behalf of patients.

The bill does not provide for payment to groups of physicians, clinics, or hospitals providing professional services.

The bill does not emphasize the desirability of full utilization and further development of existing services and facilities.

The bill does not emphasize the necessity of restricting the development and expansion of a state program to the capacity of available administrative and professional resources.

The bill does not provide the professions with a continuing authoritative voice in the formulation of policies and plans. Such committees as are selected under the provisions of the bill may represent the attitude of the administrator rather than that of a given profession or group. (This violates Basic Principle 2.)

The bill does not provide the facilities whereby the opinions of both the federal and state advisory committees are made available to the public.

Designation of the Children's Bureau as the administrative agency does not adequately assure proper integration of the health activities of the federal government.

For these reasons the Society believes that this proposed act does not represent the best form of legislation for the purposes for which it was written.

## Comment

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### THE ACADEMY GROWS UP

Certain developments at the Pittsburgh meeting evidenced that our 15-year-old child is rapidly growing up and is fast approaching maturity. During these fifteen years of infancy and childhood it has been coddled, guided, admonished, and bossed by its Evanston mother with the love that is necessary for every child during these growing years. As a result it is now ready to stand on its own feet and face the world for better or worse. To one who, as Editor of the JOURNAL, has been in close contact with the Academy for these fifteen years, there were three developments at Pittsburgh whose significance may be overlooked by many who have not had the same opportunity for observation of the child's growth. All three are, in a way, interrelated.

The first was the announcement of a new Committee for the Improvement of Child Health of nine appointed by the President, with three members to be appointed each year for a term of three years. While the primary purpose of this committee is to take over where the "Study Committee," which has been doing such a remarkable job under Dr. Sisson's chairmanship and Dr. Hubbard's Executive direction, leaves off, its importance for the future is even greater. The Academy in the past has not had a definite policy or program, but has of necessity met new developments on a specific basis and at times has been quite unprepared to grasp the significance and potentialities of the problem. This new committee is splendid in its make-up, containing outstanding leaders, and is representative of the various pediatric interests. It will not, like the Executive Board, be forced by necessity to devote most of its time to the mechanics of running the Academy which leaves little time to consider and discuss policies. The value and strength of this committee will depend in large measure upon the wisdom of the new yearly appointments made by the presidents in the future.

The second was the redistribution of the Academy on a basis of membership. The Executive Board is now comparable to the House of Representatives rather than the Senate, and hence becomes much more democratic and directly representative of the membership. Our Executive Board over these years has been made up of a splendid group of men who have been willing to sacrifice of their time and energy for the Academy. It was because of this willingness and ability to work for the Academy that they ultimately found themselves members of the Board. However, it has never been what might be regarded as representative of pediatrics as a whole. With a "policy" committee with the primary purpose of studying and considering the welfare of pediatrics, and an Executive Board to consider the welfare of the Academy, we should be able to make sound progress. The work of the two, as we said before, is closely related.

The third matter of significance was the meeting of the revamped Committee on Legislation. Its chairman has done yeoman service in the past, but has had

to go it very much alone, attempting to represent what he felt to be the opinion and policy of the Academy, when, as a matter of fact, it had no formal policy or united opinion. New and interested young blood has been added to the committee and, with the new "policy" committee as well as the Executive Board to fall back upon, the strength and importance of the Committee on Legislation have increased many, many times.

At a well-attended luncheon meeting of the Committee on Legislation, the point was made that we had no standards or criteria upon which to judge or pass an opinion on the good or bad of proposed legislation. In the discussion it was brought out that the similar point was made at a meeting of the Massachusetts Medical Society. A committee was appointed by them, reflecting all shades of social and economic thought, and this committee found itself able to agree unanimously upon certain fundamental standards or criteria by which legislative proposals should be judged. It was the feeling of everyone present at the luncheon that some such basis or standards should be made for the Academy. This is a matter the Editor feels to be of vital importance to the Academy. In this issue under *Social Aspects of Medicine* we have reprinted the standards adopted by the Massachusetts Medical Society and the interpretation of two bills under these standards. We feel it is most important for every Fellow to read this section. Had such standards been available and in effect a year or so ago, it would have prevented the somewhat intemperate discussions that took place.

Developments such as these give evidence that the Academy is approaching maturity.

B. S. V.

# The Journal of Pediatrics

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## Original Communications

### THE CLINICAL USE OF HYALURONIDASE IN HYPODERMOCLYSIS

OSCAR HECHTER, PH.D., SHREWSBURY, MASS., SAUL K. DOPKEEN, M.D.,  
AND MILTON H. YUDELL, M.D., WORCESTER, MASS.

THE purpose of this report is to describe the clinical use of the enzyme hyaluronidase to facilitate the administration and absorption of large volumes of fluid given by hypodermoclysis.

It is now widely accepted that hyaluronidase, the mucolytic enzyme which acts on the mucopolysaccharide hyaluronic acid, is the "spreading factor" of Duran-Reynals<sup>1</sup> and McClean<sup>2</sup> (for reviews of hyaluronidase see Duran-Reynals,<sup>3</sup> Mann and Lutwak-Mann,<sup>4</sup> and Meyer<sup>5</sup>). In the absence of spreading factor, an intradermally injected indicator remains localized in a bleb from which it spreads at a slow rate; in the presence of hyaluronidase the solution spreads very rapidly, at a rate dependent mainly upon enzyme concentration, to an area determined principally by the volume of injection.<sup>6</sup> The spreading activity of hyaluronidase is due to the removal of a tissue barrier to fluid diffusion thought to be a hyaluronic acid gel present in the ground substance of the connective tissues which the enzyme depolymerizes. The spreading reaction is so rapid with optimal enzyme concentrations, that the bleb which results following injection is completely flattened within a minute or less.<sup>3</sup> While the spreading reaction of hyaluronidase has been studied most extensively in dermis, it is known that the enzyme produces a qualitatively similar response in subcutaneous tissues, muscle, and possibly in most tissues.<sup>3</sup>

Consideration of the spreading activity of hyaluronidase suggested that the enzyme might be useful clinically as an aid in fluid and drug administration by the subcutaneous or intramuscular routes where the volume of fluid administered is large relative to the tissue spaces available. Since the enzyme promotes rapid spreading, pain resulting from tissue distention produced by the injection of large volumes of fluid should be prevented or reduced. Where large volumes of fluid must be injected, hyaluronidase should increase the rate of fluid administration, since the injected fluid does not remain localized at the site of injection. Finally, the rate of circulatory absorption of the constituents of the injected fluid should be increased by hyaluronidase, since the

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injected material is in contact with a greater number of absorptive channels (capillaries and lymphatics) by virtue of the spreading produced by the enzyme.

While these actions of hyaluronidase suggest that the enzyme might be useful in a number of clinical problems involving fluid and drug administration, one instance where hyaluronidase appeared to offer special promise is in the facilitation of hypodermoclysis (first advocated by Sannella<sup>7</sup>). This method of fluid administration, as is well known, is painful, time consuming, and the administered fluid is generally absorbed at a slow rate. Despite the known disadvantages of hypodermoclysis, this procedure remains an important method for administering large volumes of fluid, particularly to infants and young children.

An investigation was therefore undertaken to study the possible clinical usefulness of hyaluronidase as an aid in hypodermoclysis. The investigation was carried out in the following steps. First, the effect of hyaluronidase on the administration of large volumes of fluid subcutaneously was studied in guinea pigs and rabbits. After it had been determined that hyaluronidase markedly facilitates the administration of subcutaneously administered fluid in experimental animals, hyaluronidase was administered to normal adult human volunteers to determine whether the enzyme produced untoward reactions. Finally, after it was determined that hyaluronidase was nontoxic to humans, it was administered to patients receiving hypodermoclysis.

#### EXPERIMENTAL

The spreading enzyme used in these experiments was a bovine testis hyaluronidase preparation prepared by the method of Madinaveitia,<sup>8</sup> and furnished as a dry powder by the Schering Corporation. The preparation contained approximately 20 turbidity-reducing units per milligram as evaluated by the assay method of Kass and Seastone.<sup>9a</sup> In most instances the enzyme was used directly after dissolution in 0.85 per cent sodium chloride, but in other instances a sterile enzyme solution which had been stored in the refrigerator for varying intervals of time ranging from one to four weeks was employed. The hyaluronidase preparation utilized in these studies is antigenic as evaluated by tests on guinea pigs and rabbits.

*Effects of Hyaluronidase Upon Clysis in Guinea Pigs and Rabbits.*—Although Sannella<sup>7</sup> has reported that testis hyaluronidase administered in conjunction with saline clysis in rabbits significantly increased the rates of fluid administration and absorption, the variability of the results obtained in his study does not provide strong evidence for these conclusions.

It seemed necessary, therefore, to reinvestigate the effect of hyaluronidase upon the administration of fluid subcutaneously. In an attempt to eliminate variations between animals, the effect of hyaluronidase was first compared by giving clysis with and without enzyme into the hind legs of the same animal. This procedure, however, was still not satisfactory, for it was observed that the position of the needle under the skin influenced the rate of fluid administration to a large degree. Since it is impossible to determine when two hypodermic needles are subcutaneously placed in exactly the same position relative to

tissue elements, the following procedure was adopted to eliminate variations due to point of injection: saline was administered by drip hypodermoclysis at a constant hydrostatic pressure; the hypodermic needle was fixed in place with adhesive tape and the rate of fluid entry was determined; after the rate of fluid intake became constant, hyaluronidase was then injected into the rubber tubing connecting the needle and the fluid reservoir without disturbing the position of the hypodermic needle. The change of fluid entry induced by hyaluronidase was noted, and the character of the swelling produced by saline administration before and after hyaluronidase administration was observed.

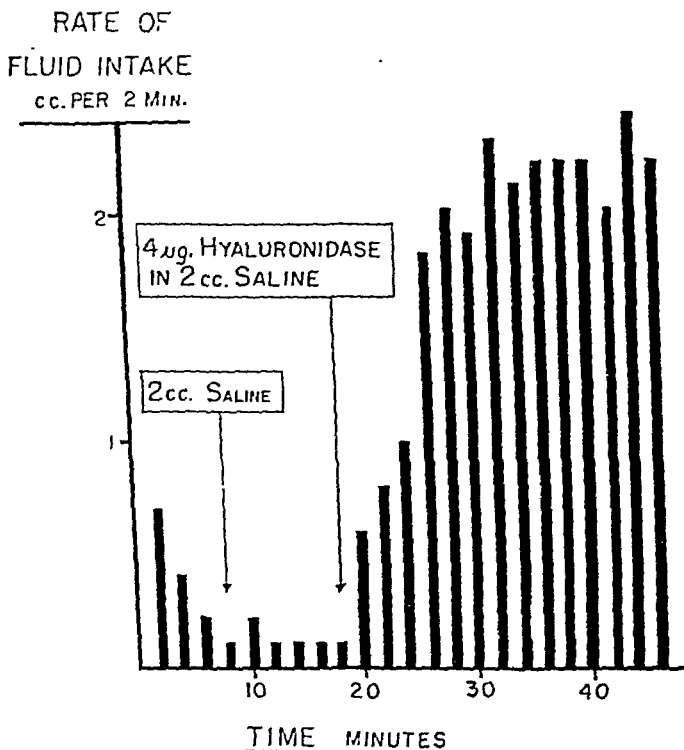


Fig. 1.—A typical experiment illustrating the intake of physiologic saline by the subcutaneous tissues of a guinea pig, in the presence and absence of hyaluronidase. At constant hydrostatic pressure (60 cm. of water) fluid was run into the tissues via a 26-gauge needle from a reservoir. It will be seen that the rate of fluid intake decreased in a short time as the injected area filled with fluid. When saline was injected into the rubber tubing connection between the needle and reservoir, no effect on fluid intake was obtained. When, however, 4  $\mu$ g. of hyaluronidase were injected into the rubber tubing, the rate of fluid intake rapidly increased and this was maintained for the duration of the experiment.

The result of a representative experiment in a guinea pig, using the above procedure, is illustrated in Fig. 1. In this experiment, the hydrostatic pressure was held constant at 60 cm. of water, a 26-gauge needle was placed subcutaneously in one of the front paws; and the volume of fluid administered per two-minute interval was measured. Under these conditions, saline entered the subcutaneous tissues initially at a rate of 0.35 c.c. per minute in the first two minutes and then declined, so that after ten minutes the fluid intake was near zero. At this point it was noted that the injected fluid had formed a raised,

hard lump, well circumscribed around the point of injection. The pressure within the injected area of skin was almost sufficient to completely offset the hydrostatic pressure of the injection. To control the effect of an injection into the rubber tubing connection between the needle and the burette upon the rate of fluid entry, 2.0 c.c. of saline were then injected into the rubber tubing. It will be seen that the injection of saline alone had no effect in increasing the rate of fluid administration during the next ten minutes. Then 2.0 c.c. of saline containing 4  $\mu$ g. of hyaluronidase were injected into the rubber tubing connection. Immediately the rate of fluid intake was increased, and after six minutes had increased approximately three times over the initial rate of administration, i.e., before resistance due to the distention was established. After the introduction of hyaluronidase, the injected area, which had been hard and well circumscribed, became soft, easily movable, and spread considerably. During the next twenty minutes in which measurements were made, it was observed that the rapid rate of fluid administration induced by the enzyme was maintained.

This typical experiment demonstrates that the barrier to rapid diffusion in the subcutaneous tissues of the guinea pig can be removed by minute amounts of hyaluronidase, and thus the administration of fluid is facilitated. The effect of hyaluronidase to facilitate fluid administration can be evaluated in either of several ways. For example, during the twenty-four-minute interval after 4  $\mu$ g. of hyaluronidase have been introduced, 22 c.c. of saline were administered; this represents a rate of administration equivalent to 0.92 c.c. per minute. In the absence of hyaluronidase, the average rate was 0.2 c.c. per minute. On this basis of comparison, the rate of fluid administration was increased 4.5 times by hyaluronidase. Perhaps a better manner of evaluating the effect of hyaluronidase would be to compare the time necessary to administer equivalent large volumes of saline in its presence and absence. To administer a volume of 22 c.c. of saline with hyaluronidase, twenty-four minutes was required; without hyaluronidase, it would have required approximately six hours to administer the same quantity of fluid, assuming that the rate of fluid intake in the absence of enzyme remained constant. On this basis, hyaluronidase increased the rate of fluid administration more than twelve times.

In seven other experiments using the above technique in guinea pigs, it was observed that maximal spreading effects were produced by the administration of 1 to 5  $\mu$ g. of enzyme, as evidenced by the fact that subsequent addition of 100  $\mu$ g. of hyaluronidase did not increase the rate of fluid intake over and above the rise induced by the initial dose. In five guinea pigs, minimal effects were produced by doses of 0.05 to 0.1  $\mu$ g. of hyaluronidase.

In general, it was observed that the effect of hyaluronidase to facilitate clysis was significantly influenced by the resistance or the "tightness" of the tissues. When the initial resistance was high, hyaluronidase produced the largest increases in the rate of administration over the initial values. When the skin was "loose" (and the initial resistance was low) and the rate of fluid entry in the absence of enzyme was high, hyaluronidase, while acting, produced less

effect on the rate of fluid intake. This proved to be true with both rabbits and guinea pigs but this effect of hyaluronidase action in the subcutaneous tissues is best observed in comparing guinea pigs to rabbits. In the former species the subcutaneous administration of saline led to hard, tight swellings which did not spread readily as the injection was continued. In rabbits, the subcutaneous administration of saline without enzyme led to the development of softer, less well-circumscribed swellings, which spread much more easily than in the guinea pig.

*Toxicity Studies on Hyaluronidase in Normal Humans.*—With the demonstration that microgram doses of hyaluronidase markedly facilitate clysis in experimental animals, it was necessary, before clinical trial in patients, to test the possible toxicity of the enzyme preparation available to us. After preliminary testing satisfied us that our hyaluronidase preparation given in doses equivalent to 50 to 200 mg. per kilogram in guinea pigs and rats, and 20 to 50 mg. per kilogram in rabbits produced no toxic reactions, hyaluronidase was administered to twelve normal human volunteers (nine men and three women), in amounts assumed to be much higher than the doses which would be necessary for clinical use in hypodermoclysis. In the first test, seven adult males received 2 mg. hyaluronidase in a volume of 1.0 c.c. intradermally in one arm and 1 c.c. saline in the other arm as a control. Following the administration of 2 mg. of enzyme, no significant change in the complete blood count was noted during the following week. Blood pressure and pulse were not affected and no toxic action of hyaluronidase was evident. The only untoward effect evident was that in four of the seven subjects a dull aching pain associated with slight erythema developed at the sight of injection several hours after administration of hyaluronidase. The local reaction persisted for a variable period of time, but disappeared in twenty-four hours. The local reactions observed were in no way similar to the reactions characteristic of allergic hypersensitivity, which developed in a short time (fifteen to thirty minutes), exhibit a characteristic wheal with pseudopodia and a red flare on the periphery of the wheal, and are associated with itching. The local reactions observed in these patients injected with hyaluronidase were of a type commonly associated with the injection of foreign protein. Since the hyaluronidase preparation we utilized is only partially purified, and undoubtedly contains inert bovine testis protein, this result is not surprising.

In the next experiments, the effect of enzyme concentration upon spreading activity was studied in six normal adults to determine whether significant spreading activity could be obtained with dilutions of enzyme insufficient to produce the local foreign protein reaction. Three men and three women received separate intradermal injections of 0.2 c.c. of solutions of hyaluronidase varying from 1,000 to 0.1  $\mu$ g. per cubic centimeter, in separate areas of the two arms. The time of wheal disappearance was utilized as a measure of hyaluronidase spreading activity and any local reactions which developed following injection were noted. Table I illustrates the results obtained. It will be seen that, while hyaluronidase in all of the concentrations used decreased the time of wheal disappearance over the appropriate saline control, as the concentration is increased,

TABLE I. THE SPREADING ACTIVITY AND THE LOCAL SKIN REACTIONS PRODUCED BY VARYING CONCENTRATIONS OF HYALURONIDASE IN ADULT HUMAN BEINGS

HYALURONIDASE ( $\mu$ G. PER C.C.*)	NO. SUBJECTS	MEAN TIME OF WHEEL DISAPPEARANCE (MIN.)	"FOREIGN PROTEIN" SKIN REACTIONS RESULTING FROM INJECTION OF HYALURONIDASE		
			SEVERE	SLIGHT	ABSENT
1000	6	$0.20 \pm 0.06$ †	3	2	1
100	6	$0.78 \pm 0.17$	0	1	5
10	6	$3.0 \pm 0.70$	0	0	6
1	6	$6.1 \pm 1.20$	0	0	6
0.1	6	$15.0 \pm 5.6$	0	0	6
0	6	$65.0 \pm 8.4$	—	—	—

\*All injections were administered intradermally in a volume of 0.2 c.c. of 0.9 per cent NaCl.

†Standard error of the mean.

the spreading response tends to approach a maximal value. Thus, while there is a large difference in time of wheal disappearance obtained by increasing the dosage from 0 to 0.1  $\mu$ g. per cubic centimeter there is a progressively smaller increase in spreading as dosage is increased, so that there are only small differences between 100 and 1,000  $\mu$ g. per cubic centimeter of enzyme. Of interest in this connection was the simultaneous finding that while local foreign protein reactions occurred in five of the six subjects receiving 1,000  $\mu$ g. per cubic centimeter enzyme, there was only one case in which a local reaction was observed using the 100  $\mu$ g. per cubic centimeter concentration, and none with the 10  $\mu$ g. per cubic centimeter dose, despite the fact that almost equivalent spreading effects were obtained with the lower dosages.

TABLE II. THE FAILURE OF A TESTIS HYALURONIDASE PREPARATION TO PRODUCE .  
HYPERSENSITIVITY IN SEVEN ADULT HUMAN BEINGS

SUBJECT	HYALURONIDASE INJECTED		DATE OF SCRATCH TESTS*
	AMOUNT (MG.)	DATE	
1	2.0	1/ 8/45	Negative on 2/4/45, 2/28/45, 4/20/45, and 11/18/45
	0.222	4/20/45	
2	0.200	1/ 8/45	Negative 4/1/45
3	2.0	1/ 8/45	Negative 3/8/45, and 4/1/45
4	2.0	1/ 8/45	Negative 4/1/45, and 11/15/45
5	0.222	4/20/45	Negative 11/18/45
6	0.222	4/20/45	Negative 11/18/45
7	0.222	4/20/45	Negative 11/18/45

\*The solution used in the scratch tests contained 2.0 mg. per cubic centimeter of bovine testis hyaluronidase.

To determine whether the doses of hyaluronidase administered to our group of human beings produced hypersensitivity, "scratch tests" using a 2 mg. per cubic centimeter solution of bovine testis hyaluronidase were performed on seven subjects who had received hyaluronidase two to ten months previously. The results, shown in Table II, demonstrate that the bovine testis hyaluronidase given in amounts ranging from 2.222 to 0.222 mg. hyaluronidase was not antigenic in adult human beings.

*Further Studies to Test Possible Toxicity of Hyaluronidase.*—Although the above findings demonstrated that hyaluronidase, in the doses administered, was nontoxic and nonantigenic in normal adult human beings, before using hyaluronidase

dase clinically it was necessary to obtain information concerning the following additional points: (a) the minimal enzyme concentration required to facilitate absorption and administration of subcutaneously injected fluid in humans; (b) the duration of time necessary to reconstitute the tissue barrier to fluid diffusion removed by hyaluronidase; (c) the effect of a hyaluronidase clysis upon a distant localized infection, since it is possible that hyaluronidase, which facilitates spreading of bacteria as well as fluids, might promote the invasiveness of the bacteria and thus enhance the pre-existing lesion; (d) the possible toxicity of hyaluronidase in a patient with lowered resistance in contrast to an individual with normal resistance.

Information concerning (a), (b), (c), and (d) was obtained from studies in a congenital hydrocephalic patient who had localized infections. As is well known, hydrocephalics have a decreased resistance to infection and other stresses.

CASE 1.—A white female congenital hydrocephalic, hospitalized in the Pediatric ward at Hahneman Hospital since birth, weighed 6 lbs., 12 oz., eight days after delivery, and had a head measurement of 15 inches. At the time the study was initiated, the patient (103 days old) weighed 12 lbs., 8 oz., and the head measurement was 24 inches. While the patient took feedings well, the increase in body weight seemed to be due primarily to the increased fluid within the head, since the body size or development did not otherwise appreciably increase. The skin of the extremities was extremely thin and "loose" (it could readily be picked up). The patient had a noninfected meningocoele on the spine, and had bilateral infected decubitus ulcers on the parietal regions of the head. The infectious processes had been controlled prior to the initiation of the study by frequent boric acid irrigation and the application of dry merthiolate dressings. During the period of thirty-one days that this patient lived, four clysis with varying doses of hyaluronidase were administered and compared to comparable clysis in the absence of enzyme. The fluid administered in all instances was 5 per cent glucose in 0.85 per cent saline. During this interval, a complete blood count was taken daily and rectal temperature measurements made thrice daily. The infected areas on the head were noted carefully to determine whether hyaluronidase clysis at a site distant from the lesion promoted spreading of the infection.

To determine the influence of hyaluronidase upon facilitation of clysis, varying concentrations of enzyme were administered subcutaneously into one subscapular region. Leaving the needle in place, 50 c.c. of dextrose-saline was then injected subcutaneously into the enzyme-treated area. The time required to administer this volume of fluid using maximal pressure, the character of the lump produced by injection, and the time required for the complete disappearance of the injected swelling were noted and compared to the results obtained following the injection of 50 c.c. dextrose saline into the opposite shoulder.

The effect of 2,000  $\mu$ g. hyaluronidase injected in a volume of 2 c.c. was first studied. Using this dose of enzyme in the right shoulder, it was observed that the injection was completed in 75 seconds; the area after injection was soft and easily movable, no seepage of fluid from the injection hole was noted, and the fluid spread within ten minutes so completely that there was no swelling indicative of injection. In the other shoulder, which had not been treated with enzyme, the time required for fluid administration was 2.5 minutes, the injected area was hard and tense, fluid oozed out at the point of injection, and the fluid was "absorbed" in 60 to 90 minutes. After one week, the effect of a 20  $\mu$ g. dose of hyaluronidase in facilitating clysis was studied. One week later, the effect of a 2  $\mu$ g. dose was similarly determined. It was observed that the 20  $\mu$ g. dose produced an effect equivalent to the 2,000  $\mu$ g. dose; the 2  $\mu$ g. dosage produced only a questionable effect to facilitate hypodermoclysis.

The duration of the hyaluronidase action to facilitate spreading was determined by reinjecting the enzyme-treated areas at twenty-hour intervals with 50 c.c. physiologic

saline and noting whether the clysis was administered easily, produced a soft swelling which spread readily, and was absorbed within fifteen to twenty minutes. The injection of a single, 2,000  $\mu$ g. dose of enzyme facilitated clysis five days but not seven days after the initial enzyme injection. With the 20  $\mu$ g. dose of enzyme, it was observed that the hyaluronidase effect to facilitate clysis was evident twenty-four hours after the initial injection, but unfortunately the entire duration of the residual activity of the enzyme could not be determined. The 2  $\mu$ g. dose, which produced only a questionable hyaluronidase response on the initial clysis, had absolutely no effect on a second clysis given twenty-four hours later.

In another test, the effect of 20  $\mu$ g. hyaluronidase upon the rate of administration of hypodermoclysis was quantitatively determined. Saline-dextrose solution was administered by drip clysis from a graduated fluid reservoir into the thigh by a nurse who had no knowledge of the experiment. Without enzyme, 100 c.c. of fluid was administered in forty-five minutes, and it was necessary to stop the clysis four different times for varying intervals of time to permit fluid absorption. After the subcutaneous injection of 20  $\mu$ g. of hyaluronidase into the other thigh, 100 c.c. of fluid was administered in twenty-five minutes, and it was not necessary to either slow or stop the clysis. As in the previous clysis with hyaluronidase, the injected areas were soft, spread easily, and the fluid was absorbed more rapidly as compared to the area injected with fluid without enzyme. Thus with hyaluronidase the rate of fluid administration was increased approximately twofold. However, as had been previously mentioned, the extremities of this subject were very poorly developed and the connective tissues loose. Thus, the fluid ran in easily without hyaluronidase, a circumstance which has been previously pointed as tending to decrease the effect of hyaluronidase in this reaction.

During the course of the month, during which four hyaluronidase clyses were performed, a total of 2,022 mg. of hyaluronidase was administered, no significant change due to the enzyme was observed upon the red blood count, white blood count and differential, hemoglobin, or the color index. The temperature remained unaffected. No local reactions of any type developed with any of the enzyme dosages employed, and no untoward results were noted. It was of special interest that the infected decubitus ulcers on the head were in no way affected by the hyaluronidase clysis administered either in the shoulders or the thighs. Finally, the patient died a noninfectious, hydrocephalic death, ascribed to inanition.

This case demonstrates that hyaluronidase clysis administered in an area distant from localized infection does not lead to spreading of the infection. Further from this study it appears that the order of magnitude of the optimal dosage of hyaluronidase is about 20  $\mu$ g., since increasing the dosage 100 times did not appear to produce a significantly greater response, and decreasing the dose to 2  $\mu$ g. produced only a questionable effect. In view of the results shown in Table II, wherein 2,220  $\mu$ g. of the enzyme preparation failed to be antigenic, it may be inferred that the administration of 20  $\mu$ g. of bovine testis hyaluronidase should not lead to hypersensitivity in patients treated with hyaluronidase clysis.

*Effect of Hyaluronidase in Hypodermoclysis in Patients.*—Thereafter, hyaluronidase was utilized successfully in two additional patients.

CASE 2.—A 9-month-old white male was admitted to the hospital with a diagnosis of infectious diarrhea. The patient was severely dehydrated and M/6 sodium lactate clysis was ordered. Using the usual technique for drip hypodermoclysis, without hyaluronidase only 75 c.c. could be run into the thigh of one leg in four hours. In the other thigh, 20  $\mu$ g. of hyaluronidase was injected subcutaneously in a volume of 1 c.c. Immediately thereafter, the syringe was withdrawn, leaving the needle in place, and the needle was then attached to the clysis outfit. In the presence of hyaluronidase, 150 c.c. were administered in sixty minutes. The following day clysis was repeated, and although no measurements were taken, it was observed that the thigh which received hyaluronidase twenty-four hours previously, still showed a hyaluronidase effect in that the fluid ran in quickly, and injected area was soft, and the fluid was rapidly spread and absorbed. Following treatment with sulfaguandine, penicillin, and fluids, the patient made an uneventful recovery, and was discharged.

CASE 3.—A 9-month-old obese white male was admitted to the hospital with a temperature of 103° F. at 10:22 P.M. The patient had five convulsions lasting from one to twenty-five minutes prior to admission. Physical findings were negative except for hyperpnea and slight cyanosis of the lips. He was sedated with phenobarbital and chloryl hydrate, and there were no further convulsions. Treatment with penicillin was instituted (20,000 Oxford units intramuscularly every three hours). Drip hypodermoclysis of saline-dextrose solution, administered in the usual way without hyaluronidase, was instituted into the two thighs, but only 50 c.c. could be administered in a two-hour period. Hard lumps were noted at the injection site, and it did not appear that the injected fluid was absorbed. The patient failed during the next six hours so that at 4:30 A.M. he was in extremis, semicomatose, with a temperature of 106° F.; the pulse was feeble, the heart beat was hardly detectable, and there was peripheral circulatory collapse with generalized cyanosis. In an attempt to administer fluid intravenously, a "cut down" was performed but failed because of the patient's obesity and the peripheral vascular collapse. At 6 A.M., with the patient approaching death, 10 µg. of hyaluronidase was injected subcutaneously into each thigh, and leaving the needles in place, drip hypodermoclysis was instituted. Within fifty-five minutes, 400 c.c. of saline-dextrose was administered into the thighs. The injected areas were soft, spreading was diffuse, and the fluid was readily absorbed within thirty minutes. Thereafter, treatment with aqueous adrenal cortical extract (Upjohn) was initiated. Initially the dose was 1 c.c., administered subcutaneously every hour. After two hours, the dosage was increased to 1 c.c. per thirty minutes, and then after two more hours, the dose was increased to 2 c.c. every thirty minutes.

Within four hours after the completion of the 400 c.c. clysis, the peripheral circulation of the patient was much improved, as evidenced by disappearance of cyanosis, an increase in skin temperature and pulse. At 11:30 A.M., despite the circulatory improvement, the patient was still semicomatose. At 6 P.M. the patient was comatose but exhibited further circulatory improvement over his condition at 11:30 A.M. At this time, petechia of the pelvis and groins were observed in association with ecchymotic spots on the left knee and a clinical diagnosis of meningococcus infection with hemorrhage in the adrenals was made. 300 c.c. of saline-dextrose solution containing 5 Gm. sodium sulfadiazine was then administered by drip clysis into the areas previously treated with hyaluronidase. This clysis was completed within two hours. Again the injected areas were soft, spreading was diffuse, and the absorption of the fluid was rapid. Treatment with adrenal cortical extract and penicillin was continued. Although the peripheral circulation was well maintained, the patient remained comatose and at 2 A.M. of the next morning the child expired. Post-mortem examination confirmed the clinical diagnosis, and there was no evidence that the hyaluronidase produced a toxic reaction or contributed to the death of the patient.

#### DISCUSSION

The enzyme, hyaluronidase, possesses a variety of biologic activities and has been related to numerous processes ranging from bacterial invasiveness to fertilization of the mammalian ovum.<sup>3</sup> Thus, hyaluronidase not only produces the spreading reaction, but in addition has the activity to (a) decapsulate certain strains of streptococci,<sup>9</sup> (b) remove the cumulus cells surrounding the ovum of the rabbit,<sup>10, 11</sup> and (c) decrease the viscosity of synovial fluid.<sup>5</sup> Attempts to utilize hyaluronidase clinically have been initiated but as yet have wherein the viscosity of the exudate appeared to be increased, lowered the viscosity of the exudate without permanently improving the pathologic condition.<sup>12</sup> Hyaluronidase has been successfully used for paracentesis in a case



of mesentelioma of the pleura and peritoneum to facilitate the removal of a fluid of honeylike consistency.<sup>5</sup> It has been asserted that hyaluronidase was successfully used to induce pregnancy in certain cases of sterility.<sup>13</sup> The details of this work have been published in *The American Journal of Medicine* 1: 491, 1946.

In this study, the spreading activity of hyaluronidase has been successfully utilized to facilitate clinical hypodermoclysis. The results demonstrate that microgram amounts of a preparation of hyaluronidase facilitate the administration and absorption of subcutaneously administered fluid in both man and experimental animals. This effect of hyaluronidase seems to be dependent upon the state of the subcutaneous connective tissues. Thus when the connective tissues are loosely organized, as was the case in rabbits and our hydrocephalic patient, hyaluronidase increased the rate of administration about twofold. In guinea pigs and two patients where the subcutaneous connective tissues were well developed, the rate of fluid administration was increased to a much greater extent by the subcutaneous administration of hyaluronidase prior to clysis. While quantitative evaluation of the effects of hyaluronidase to increase circulatory absorption was not possible, an indirect, qualitative method, based upon the disappearance of the localized swelling produced by the injection of large volumes of fluid, clearly demonstrated that the enzyme promoted absorption. Thus, the swellings produced by clinical hypodermoclysis in enzyme-treated areas disappeared within ten to twenty minutes after cessation of injection, while in the absence of hyaluronidase sixty to ninety minutes were required. Inasmuch as the clinical trials of hyaluronidase were in infants, no information concerning the effect of enzyme in reducing the pain of hypodermoclysis was obtainable. While the patients appeared to be less troubled by clysis in hyaluronidase-treated areas, direct evidence that hyaluronidase prevents pain due to distention produced by fluid administration was obtained in our studies with normal adults who received an intradermal injection of 1.0 c.c. saline, with and without hyaluronidase. Without enzyme, this volume of fluid introduced intracutaneously produced intense pain which persisted for ten to fifteen minutes, while the same volume administered with hyaluronidase produced no pain at all. Further work with older children and with adults will be necessary to determine whether the pain resulting from distention produced by clysis is completely or only partially removed by hyaluronidase. Our studies demonstrate that the administration of 0.2 to 2.2 mg. of hyaluronidase to human volunteers, or 10 to 100 times the dosage required for clysis, failed to induce hypersensitivity in seven adult human beings. Thus, the effect of hyaluronidase in facilitating clinical hypodermoclysis is obtained with such small doses of enzyme extract (approximately 10 to 20  $\mu$ g.) that no hypersensitivity to testis protein results, although the enzyme preparation available to us is antigenic in guinea pigs. While admittedly it would be clinically desirable to have available a non-antigenic hyaluronidase preparation, this possibility remains for further biochemical investigation. In the meantime, the enzyme in its present degree of purity would appear to be suitable for further clinical trial.

Since hyaluronidase promotes spreading of bacteria, as well as the fluids used in elysis, the finding that hyaluronidase elysis in one of our patients did not enhance a pre-existing localized infection at a site distant from the injected area is important, since it demonstrates that the presence of a localized infection does not contraindicate the use of enzyme as an aid in elysis. This clinical result confirms the previous findings of Sannella<sup>7</sup> who demonstrated that hyaluronidase-saline elysis failed to enhance an experimentally induced *Staphylococcus aureus* infection in rabbits. An explanation for the failure of a hyaluronidase elysis to affect a localized infection is afforded by the finding that hyaluronidase injected into normal skin diffuses around, but not through, an area of skin containing a fibrin barrier.<sup>14</sup> This result, taken together with the finding that hyaluronidase injected directly into an area containing fibrin can penetrate the barrier, demonstrates that enzyme injected into normal skin diffuses in a path of least resistance and consequently does not pass through an area of skin containing a fibrin barrier. Since the localization of bacteria is due in large part to fibrin deposition in the lymphatics and the interstitial spaces in infected skin,<sup>15</sup> an explanation for the absence of any hyaluronidase effect upon a pre-existing localized infection is evident.

While this report has dealt with the usefulness of hyaluronidase in facilitating the subcutaneous administration of large volumes of salt solutions (with and without glucose), hyaluronidase may also be useful for the subcutaneous administration of large amounts of plasma and drugs. We have found that in newborn infants the swellings produced by the subcutaneous injections of 30 c.c. amounts of plasma with hyaluronidase disappear within sixty minutes; without enzyme, six to twenty-four hours are required before the swellings disappear. While as stated previously, it is not possible to deduce accurately from this type of data the rate of circulatory absorption of the subcutaneously administered plasma, it seems clear that plasma absorption is likewise facilitated by hyaluronidase. This finding may be of some importance in those clinical conditions such as infectious diarrhea, where plasma must be administered, and where recourse to the intravenous route is difficult.

#### SUMMARY

1. Microgram amounts of a bovine testis hyaluronidase preparation markedly facilitates the administration of hypodermoclysis in experimental animals.
2. The administration to human volunteers of milligram amounts of the hyaluronidase preparation produces no toxic reactions aside from a nonspecific transient foreign protein reaction. These reactions do not occur when the dosage is decreased to 200  $\mu$ g.
3. Milligram doses of enzyme did not produce hypersensitivity to bovine testis proteins in the volunteer subjects, although the preparation in larger doses is antigenic in guinea pigs.
4. In three patients, hyaluronidase administered subcutaneously in a dosage of 10 to 20  $\mu$ g. markedly increased the rates of absorption and administration of hypodermoclysis with no untoward reactions.

5. In one patient, the administration of hyaluronidase elysis did not influence a pre-existing localized infection.

6. In another patient with circulatory collapse, the circulation was restored successfully after ordinary hypodermoclysis and an attempted "cut down" for intravenous administration failed.

7. It is suggested that hyaluronidase deserves further clinical trial and study as an aid in hypodermoclysis.

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## LUNG CALCIFICATIONS AND HISTOPLASMIN-TUBERCULIN SKIN SENSITIVITY

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RECENT studies have demonstrated a relationship between histoplasmin skin sensitivity and lung calcification. As a part of the Fels Research Institute's longitudinal study of 200 normal southwestern Ohio children, chest x-rays and skin sensitivity tests have been done. Because of the serial nature of this research program, which includes these yearly chest x-rays from birth, certain of the data seem peculiarly suited to a study of the relationships of histoplasmin skin sensitivity to lung calcification and other factors.

In the past ten or fifteen years there has been an increasing interest in the etiology of pulmonary calcification. There have been many reports in the literature concerning the discrepancy between tuberculin-positive skin reactions and the presence of pulmonary calcifications. It has been shown<sup>1-3</sup> that from 27 to 83 per cent of young individuals, living for the most part in or adjacent to the eastern slope of the Mississippi River basin and the bordering states of the western slope, have demonstrable pulmonary calcification previously accepted by most roentgenologists as indicative of healed primary tuberculosis. Yet, less than one-half of the individuals with lung calcifications were found to have positive tuberculin reactions.

Thus, the classification of the significance of lung calcifications has remained a challenge to investigators. Several years ago, Cox and Smith<sup>4</sup> and Aronson and associates<sup>5</sup> showed that coccidioidomycosis could produce pulmonary lesions which calcify and produce x-ray findings identical with those of primary pulmonary tuberculosis. However, the occurrence of coccidioidomycosis seems to be limited for the most part to certain areas of the west. Christie and Peterson<sup>1-3</sup> and Palmer<sup>6</sup> have shown that there is a high correlation between positive histoplasmin cutaneous sensitivity reactions and the presence of pulmonary calcifications in individuals who do not react to tuberculin. These findings are in accordance with the suggestion of Smith<sup>7</sup> that histoplasmosis occurs most frequently in those areas in which the incidence of pulmonary calcification with negative tuberculin reactions is high. They have suggested that apparently a nonfatal form of histoplasmosis does occur and can produce intrathoracic calcifications. They have further shown that in their series the incidence of positive histoplasmin reactions far outnumbers the incidence of positive tuberculin reactions in individuals with pulmonary calcifications. Observations by these investigators have also shown that some individuals with pulmonary calcifications react neither to tuberculin nor to histoplasmin. The purpose of this paper is to present further observations pertinent to the problem

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of lung calcification. Along with incidence of lung calcifications and positive tuberculin and histoplasmin skin reactions, it will deal with such questions as: (1) age of appearance of lung calcification; (2) age of appearance of lesion preceding calcification; (3) age difference in positive histoplasmin and tuberculin skin reactions, and the progressive changes in patterns of precalcification lesions and calcification.

TABLE I. FELS CHILDREN BY AGE GROUP SHOWING REACTIONS TO TUBERCULIN AND HISTOPLASMIN

AGE WHEN TESTED* (YR.)	NO. IN GROUP	TUBERCULIN- POSITIVE		HISTOPLASMIN- POSITIVE		TUBERCULIN- POSITIVE AND HISTOPLASMIN- POSITIVE		TUBERCULIN- NEGATIVE AND HISTOPLASMIN- NEGATIVE	
		NO.	%	NO.	%	NO.	%	NO.	%
Under 5	45	3	6.7	5	11.1	1	2.2	38	84.4
5-9	53	1	1.9	25	47.1	0	0	27	52.9
10-14	50	13	26.0	32	64.0	11	22.0	16	34.0
15-19	22	9	40.9	14	63.6	6	27.2	5	22.7
Total	170	26	15.3	76	44.7	18	10.5	86	51.1

\*No children less than one year of age were tested, and those whose parents refused skin tests were omitted from the study.

#### STUDY GROUP AND MATERIALS

The children who are studied at the Fels Research Institute are so-called "normal children." Since almost all of them have been admitted to the study prior to birth, they obviously are unselected with regard to such factors as health and growth progress. The children and their families live in cities, small towns, and rural areas. While the "Fels population" is higher than both the national average and the Ohio average in economic status, the group includes, nevertheless, children from all economic levels and from all types of homes. The age distribution is shown in Table I.

TABLE II. THE OCCURRENCE OF SENSITIVITY TO TUBERCULIN AND HISTOPLASMIN, AND THE PRESENCE OF INTRATHORACIC CALCIFICATIONS IN FELS CHILDREN

NO. EXAMINED	TUBERCULIN-POSITIVE		HISTOPLASMIN- POSITIVE		NO. SHOWING INTRATHORACIC CALCIFICATIONS	
	NO.	%	NO.	%	NO.	%
170	26	15.3	76	44.7	103	60.6

Because of the longitudinal principle of the study, serial chest x-rays have been taken on most children at 1, 6, 12, 18, and 24 months, and at yearly intervals thereafter. On some of the children the early x-rays were taken at 1, 4, 10½, 16½, and 22 months. The films are chest-size, taken at 6 feet. The serial nature of these x-rays makes possible not only a diagnosis of presence or absence of lung calcification but also a study of the progressive changes in the lung from the time of the initial lesion through the period of calcification. Often we have come to recognize the true nature of the initial lesion only when the soft tissue changes began to be supplanted by calcification. Thus, a lung marking which in a 4-month x-ray was taken for a blood vessel, may have become at 10½

months a definite spot of consolidation, and by 22 months may have begun to calcify. The serial x-rays have made it possible, therefore, to observe the nature of the initial lesion, its progress and period of existence before calcification, and to learn as well of any progressive calcification in later years or of any resorption of existing calcification.

Single x-rays of the chests of both parents have been taken, and since there are as many as seven siblings in a family, almost all of whom have been serially x-rayed and skin tested, sibling incidence of histoplasmin reactions may also be studied. Physical examinations at six-month intervals since birth, as well as continuous illness records, constitute part of the material.

All children included in the study were given first strength (.00002 mg.) Purified Protein Derivative intradermally on one arm and histoplasmin,  $\frac{1}{10}$  c.c. of 1:1,000 on the other. These reactions were read in seventy-two hours. If the tuberculin was negative, the second strength (.005 mg.) was given. If both strengths of tuberculin and the histoplasmin gave negative tests, and if pulmonary calcifications were present, the child was tested with  $\frac{1}{10}$  c.c. of 1:1,000 extract of *Haplosporangium parvum* and the same quantity of blastomycin, an extract of the fungus *Blastomyces dermatides*.<sup>\*</sup> While the x-rays of these children were taken at frequent intervals from birth on, all of the skin tests, the results of which are shown in accompanying tables, were done during the year 1946. Many additional tuberculin skin tests were done on most of these children earlier, particularly on those having heavy lung calcifications. In no instance has a tuberculin skin test found positive at one application become negative at a later one. Perhaps by chance, all of those children with heavily calcified areas and negative tuberculin tests at an early age have, in every instance, continued to have negative tests.

#### RESULTS AND DISCUSSION

One hundred and seventy children, all one year of age or older, were tested with tuberculin and histoplasmin. Twenty-six (15.3 per cent) reacted to either .00002 or .005 mg. of Purified Protein Derivative. Seventy-six (44.7 per cent) reacted to histoplasmin, 1:1,000. One hundred and three (60.6 per cent) children had demonstrable pulmonary calcifications. These results are shown in Table II. They demonstrate the greater incidence of sensitivity to histoplasmin than to tuberculin. These findings are in accord with the results of similar series reported by others,<sup>1, 2, 5</sup> and emphasize the fact that many more calcifications occur in tuberculin nonreactors than in tuberculin reactors.

In Table I the age distribution of the children in relation to their reactions is shown. These results show an increase in positive tuberculin reactions until a maximum of 40.9 per cent in the 15- to 19-year age group is reached, with the exception of the 5- to 9-year period, which shows a drop (not statistically significant). The increasing incidence of pulmonary calcifications is much more

<sup>\*</sup>This material and the histoplasmin were supplied by the United States Public Health service through the courtesy of Dr. Carroll E. Palmer, for whose help we are deeply indebted.

rapid and far exceeds the rate of increase in positive tuberculin reactions. This relationship is shown in Fig. 1. In the older age groups, however, the incidence of pulmonary calcification appears to flatten out, while the tuberculin reactions continue to increase. It is interesting to note that the incidence of calcifications with negative tuberculin and histoplasmin reactions changes little after the age of 5. This fact suggests that the etiology of these lesions is distinct from that of the tuberculin-histoplasmin groups, and is not merely a lag in the development of sensitivity to these agents. The graphic picture is very similar to Christie and Peterson's presentation,<sup>3</sup> except that the onset of the calcification exceeds the development of the histoplasmin sensitivity, in contrast to theirs,

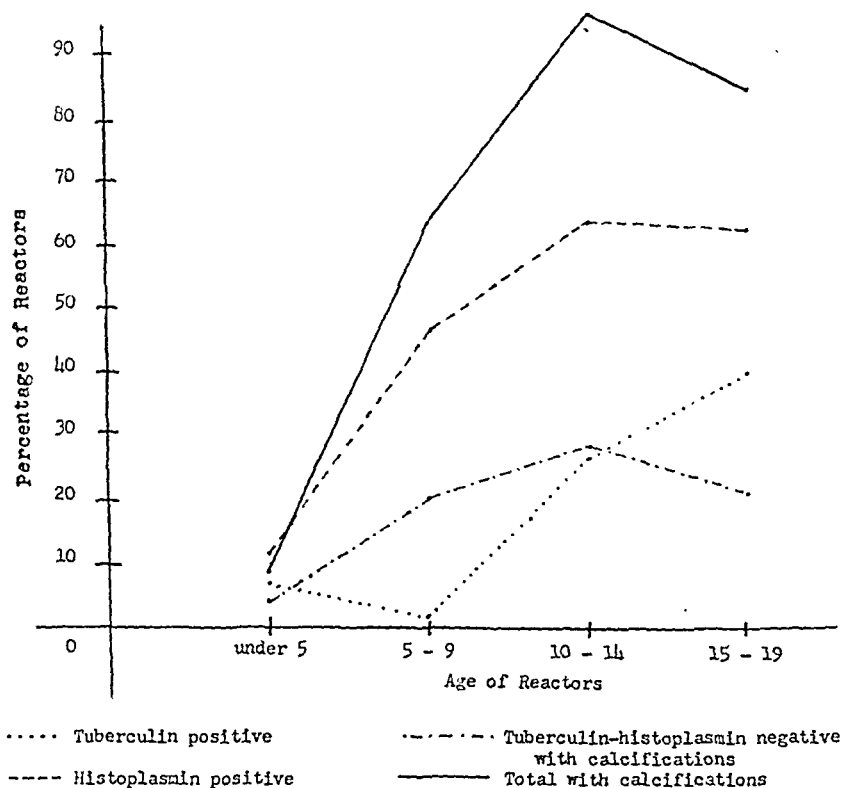


Fig. 1.

which shows a lag of calcification in relationship to histoplasmin reaction. We assume from our data either that the onset of sensitivity to histoplasmin lags behind the onset of calcification or that many calcifications are due to causes other than histoplasmosis infection. The similarity of the histoplasmin and calcification curves is striking, as is the nonsimilarity between the tuberculin and calcification curves. These same similarities and dissimilarities were emphasized by Christie and Peterson.<sup>3</sup>

TABLE III. FELS CHILDREN ACCORDING TO REACTION WITH TUBERCULIN AND HISTOPLASMIN AND THE PRESENCE OF INTRATHORACIC CALCIFICATION IN THESE REACTORS

TYPE OF REACTION	NO.	% WHOLE GROUP	NO. WITH CALCIFICATION	% REACTION GROUP WITH CALCIFICATION
Tuberculin + Histoplasmin +	18	10.6	15	83.3
Tuberculin + Histoplasmin -	8	4.7	6	75.0
Tuberculin - Histoplasmin +	58	34.1	49	84.4
Tuberculin - Histoplasmin -	86	50.6	33	38.3
Total	170	100.0	103	60.6

Table III shows the number and percentage of children according to the reactions to tuberculin and histoplasmin and the presence of calcifications in these reactors. A larger percentage of histoplasmin reactors have calcifications than do tuberculin reactors. As high an incidence of calcifications occurs in the group which are positive to both histoplasmin and tuberculin. Again these results are similar to those of Christie and Peterson. A larger percentage of our reactors have pulmonary calcifications than do those in their series. A part of this difference may be attributable to the greater ease and certainty of recognizing calcification from a series of plates. Often a calcification may show up on four x-ray films, but because of positioning or slight movement, may be doubtful on the fifth.

Table IV reveals the rather striking fact that thirty-three children with pulmonary calcifications reacted neither to tuberculin nor histoplasmin. Since all positive histoplasmin reactions yielded areas of induration and erythema of more than 5 mm., we feel that stronger strengths of histoplasmin probably

TABLE IV. HISTOPLASMIN AND TUBERCULIN REACTIONS IN 103 FELS CHILDREN WITH PULMONARY CALCIFICATION

PULMONARY CALCIFICATION AND	NO. WITH CALCIFICATION	% WITH CALCIFICATION
Histoplasmin +, Tuberculin +	15	14.5
Histoplasmin +, Tuberculin -	49	47.5
Subtotal Histoplasmin +	64	62.1
Tuberculin +, Histoplasmin +	15	14.5
Tuberculin +, Histoplasmin -	6	5.8
Subtotal Tuberculin +	21	20.3
Histoplasmin -, Tuberculin -	33	32.0

would not have resulted in a significant number of positives. We have assumed, therefore, that other etiological agents are responsible for calcifications in this group.

Table V shows the results of testing these thirty-three children with haplosporangin and blastomycin. One of these children, a girl of 14 with prominent calcifications, reacted severely to both blastomycin and haplosporangin.





Fig. 2.—The series of chest x-rays shown above pictures the changes occurring in the chest of one child from the age of 10½ months to 6½ years. A shows increase in markings in left hilus and apex and right base; B, at 22 months, shows areas of calcification in left hilus; C, at 34 months, shows round area of infiltration at left base; D, at 6½ years, shows calcification of this area plus extensive calcification of a large hilus gland on the left, apparently resulting from drainage of the previous infiltration in the left base.



*σ.*



*D.*

*(For legend, see opposite page.)*

TABLE V. RESULTS OF TESTING THIRTY-THREE CHILDREN WITH INTRATHORACIC CALCIFICATIONS, BUT WITH NEGATIVE TUBERCULIN AND HISTOPLASMIN REACTION TO HAPLOSPORANGIN AND BLASTOMYCIN

NO.	POSITIVE HAPLOSPORANGIN	POSITIVE BLASTOMYCIN
33	1	2

The child had what corresponds to a 4+ tuberculin reaction at the site of the tests. She likewise had tender axillary adenopathy, fever, and general malaise.

#### INCIDENCE IN SIBLINGS

Of the 170 children skin-tested, the majority have one or more siblings in the tested group. There are a number of families with three siblings, a few with four, and one with six children whose tests and x-rays constitute a part of our research data. It is, therefore, possible to determine whether siblings show the same reactions, either positive or negative, with greater incidence than is found in the group in general, either in terms of skin tests or calcification.

*Histoplasmin Tests.*—By pairing every sibling against each of his other siblings (108 pairs), we find that in 34 per cent of the cases when one sibling is negative the other of the pair is also. This is against an unselected group expectancy of 31 per cent. Of those pairs in which one is positive, 23 per cent showed both positive, against an unselected group expectancy of 20 per cent. By the method of Chi Square, these differences are not statistically significant.

*Calcifications.*—When one of a pair of siblings had calcification, the other had calcification in 43 per cent of the cases, against a normal expectancy of 37 per cent. When one sibling was negative, the other was also negative in 22 per cent of the cases, against an expectancy of 15 per cent. Both of these figures are statistically significant, with a probability of .02, or 2 chances in 100, that the difference is accidental. Since the histoplasmin shows no familial factor and the calcification does, its familial factor must be the result of tuberculosis and other cross-infectious conditions.

Previous to the currently accumulating knowledge of the prevalence and distribution of positive skin reactors to histoplasmin, histoplasmosis was known only as a fairly rapidly progressing, nearly always fatal disease. This fact has constituted a part of the basis for doubt as to whether positive histoplasmin skin reactors, who were not apparently ill, actually had been or were infected with the organism *Histoplasma capsulatum*. While none of the children in our group presented any symptom syndrome in any way comparable to those reported for proved acute cases of histoplasmosis, we do believe that it is premature to say that all of our cases are completely asymptomatic. There is a strong suggestion from the serial growth data and illness histories of these children that their growth progress and health pattern may be significantly different from the negative histoplasmin reactors. An analysis of any such differences will form the basis for a future paper.

#### X-RAY INTERPRETATION

The serial nature of our chest x-rays permits us to study the development of pulmonary calcifications from the precalcification or infiltrative stage to the

completely calcified lesion. As previously stated, we are able to distinguish much more clearly between false calcifications, i.e., bronchi and blood vessels on section, and artifacts, by studying the serial plates, than would have been possible had only one roentgenogram been made. Progress of the lesion, increases in density, and elimination of difficulties due to position or slight motion, all added to accuracy of determination of calcification.

Parenchymal lesions occurred much more frequently in the bases than in the apices, although they did occur in both. Initial lesions varied from fuzzy, fan-shaped extensions and exaggerations of linear markings into the periphery, to round areas of definite consolidation, often 2.5 cm. or more in diameter. Such lesions show beginning calcification twelve to fifteen months later and are heavily calcified in two or three years. Calcification of hilus glands draining such initial lesions often does not occur until two and one-half or more years later. Fig. 2 shows an interesting sequence of the progress of the lung lesions in a child strongly positive to histoplasmin but repeatedly negative to tuberculin. His 4-month x-ray (not shown) suggested a flocculent exaggeration of lung markings into the peripheries from both lung roots. From this single x-ray one could not be sure that the lung markings were abnormal. There was no hilus calcification at this time. His 10½-month x-ray (Fig. 2, A) showed quite clearly this flocculent picture extending out from the lung roots. There was a suggestion of beginning calcification in the left hilus at 16½ months. At 22 months (Fig. 2, B) there was definite calcification of the suspected area in the left hilus and an equally dense calcification in the right hilus. At 34 months (Fig. 2, C) there was a pneumonic patch of consolidation, 2 cm. in diameter, in the left base at the costophrenic angle. At 45 months this area was just beginning to calcify. At 57 months the calcification was increasingly dense but not so dense as it was at 6½ years and not nearly so dense as at 8½ years. At 6½ years (Fig. 2, D) there was first seen the beginning calcification of a large hilus gland on the left, a condition which had progressed markedly by the age of 7½ years. This large area of calcification seemed to be the result of drainage from the earlier area of pneumonic consolidation in the left base. The calcification in the left base, which was quite dense, was much smaller than the original consolidation.

This sequence of events, repeated with variations in the series of x-rays of other children, has a number of interesting implications; some of these are:

1. That the infection producing the calcification often occurs at a very early age. In our series there are nine cases in which the soft tissue changes are present at 10½ months of age. Thirty were present before the age of 24 months. Age of onset is shown in Table VI.
2. That there is a considerable lag between the initial soft tissue lesion in the parenchyma and calcification.
3. That there is often a lag of two years or more between a soft tissue lesion and a hilus calcification.
4. That the process is often a progressive one, showing new soft tissue lesions and additional areas of both parenchymal and hilus calcification over

TABLE VI. AGE AT ONSET OF PULMONARY LESION RESULTING IN PULMONARY CALCIFICATION

RESULT		NO. REACTORS	NO. CALCIFI- CATIONS	AGE ONSET LESION (MO.)				AGE ONSET CALCIFICATION (MO.)			
				0-24	25-48	49-72	OVER 72	0-24	25-48	49-72	OVER 72
Histoplasmin	+										
Tuberculin	+	18	15	4	5	4	3	0	6	3	6
Histoplasmin	+										
Tuberculin	-	58	49	10	24	10	4	4	15	18	12
Histoplasmin	-										
Tuberculin	+	8	6	3	2	1	0	2	1	3	0
Histoplasmin	-										
Tuberculin	-	86	33	13	13	4	3	3	14	10	6
Total		170	103	30	44	19	10	9	36	34	24

a period of six or more years. There are many such progressive cases in our group.

5. That calcification itself often appears very early. Of the 103 cases showing calcification, it was apparent and verifiable from later x-rays in nine cases in the first 24 months of life. In forty-five it was present at or before the 48-month x-ray.

This early calcification is in sharp contrast to the findings of Christie and Peterson, the difference probably being due to the group and perhaps partially to an increased facility of recognition by reason of our serial plates.

We attempted from our study of the serial x-rays to establish some criteria which would allow us to distinguish between the calcification patterns of the positive histoplasmin and tuberculin reactors. We were unable to do so, since identical patterns could be found in individuals who reacted to tuberculin, histoplasmin, or neither. There was, however, a tendency for calcifications associated with positive histoplasmin reactions to be: (1) multiple in the parenchyma, often with calcifications present in upper lung fields and apices; (2) early in onset, frequently with the initial lesion appearing before one year of age, the majority before 4 years of age; (3) preceded occasionally by a pneumonic infiltrate early in the infection; (4) progressive with the development of new lesions and calcifications over a period of years (eighteen of the forty-nine calcifications of the histoplasmin positive group were of this nature).

#### SUMMARY

We have presented the results of our investigations of the serial chest x-rays and histoplasmin-tuberculin sensitivity reactions in 170 essentially "normal" southwestern Ohio children. On thirty-three children with positive calcification and negative skin reactions, we have applied haplosporagin and blastomycin skin tests. We have re-emphasized the findings of other investigators that a far greater number of children are sensitive to histoplasmin than to tuberculin, and that the incidence of pulmonary calcification is much more closely associated with the incidence of histoplasmin sensitivity than with tuberculin sensitivity. There is a much closer association between the onset

of the calcification and the development of histoplasmin sensitivity than between calcification and the development of tuberculin sensitivity. A considerable number of calcifications occur in children negative to both histoplasmin and tuberculin. One of these was associated with a positive blastomycin test and one with positive haplosporangin plus a positive blastomycin test. In our series there is a tendency for familial distribution of positive lung calcifications, but not of positive histoplasmin skin reactions.

The majority of the calcifications in our study have their soft tissue changes before 48 months of age. Many of these can be traced back to the early months of life. Infiltrates and occasional round areas of consolidation are the precursors of the calcifications in the parenchyma. Progressively appearing new lesions followed by new calcifications both in parenchyma and hilus are often seen in histoplasmin-positive children over a period of several years.

#### CONCLUSIONS

1. A study of serial chest x-rays and cutaneous sensitivity to histoplasmin and tuberculin re-emphasizes the close relationship between histoplasmin reactors and pulmonary calcifications in children.

2. The onset of infections producing lung calcifications in our group is very early.

3. *Blastomyces dermatides* and *Haplosporangium parvum* may play a minor role in the etiology of pulmonary calcifications in this area.

4. Pulmonary calcifications are apparently nonspecific reactions to a variety of organisms. Cutaneous sensitivity tests and procedures other than roentgenologic must be employed to make an etiological diagnosis.

5. Pulmonary calcification in positive histoplasmin reactors is not infrequently continuous over a period of six or seven years, with new precalcarious and calcarious lesions appearing after months or years. This radiologic picture suggests that the activity of the histoplasmin organism in the body may remain active for very long periods.

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## CEPHALIN-CHOLESTEROL FLOCCULATION IN PREMATURE INFANTS AND CHILDREN RECEIVING IMMUNE GLOBULIN

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SINCE Hanger<sup>1</sup> first described the cephalin-cholesterol flocculation for aid in diagnosis of liver disorders, its use for this purpose has become extensive. There are, however, many factors which may influence the test, producing positive results. Exposing the mixed material to light,<sup>2</sup> marked changes in temperature, including refrigeration of the serum,<sup>3</sup> failure to prepare fresh cephalin-cholesterol solution, and the presence of traces of heavy metal or strong acids, will give erroneous flocculation. In pediatric practice, we are confronted with at least two other examples of a positive test being obtained where no liver damage has been found. The first and most common example is in reference to the serum of the newborn. Salmon and Richman<sup>5</sup> demonstrated that the flocculation was positive in all newborn infants studied, and remained so during the first week. These workers found that the mother's serum also gave positive results during this same period. There was no relation to icterus or general condition of these infants, and the reaction became negative at approximately the same time in each. All the reported infants were full term and weighed above 2,500 Gm.

It was decided to try the flocculation on the blood of a limited number of premature babies. Blood for the experiment was obtained from the external jugular vein. The test was performed as described by Hanger, using 0.2 c.c. of a cephalin-cholesterol emulsion. This emulsion was prepared from a cephalin-cholesterol mixture dispensed by Wilson Laboratories, Chicago, Ill. The mixture contains 100 mg. of partially oxidized cephalin and 300 mg. of cholesterol. It was dissolved in 8 c.c. of anesthesia ether and 1 c.c. of the ether solution was added to 35 c.c. of distilled water. The aqueous emulsion then was allowed to simmer below boiling until a final volume of 30 c.c. was reached. This emulsion was brought to room temperature before using and was prepared on the day the tests were performed. After adding 1 c.c. of the emulsion to the diluted serum, the solution was placed in a dark place at room temperature and flocculation was noted in twenty-four and forty-eight hours. One plus to 4+ reactions were recorded, depending on how clear the supernatant fluid appeared. A 4+ reaction was recorded when all the cephalin-cholesterol had settled to the bottom of the tube.

The results, which were rather inconsistent, are shown in Table I. All the sera from these premature infants gave positive tests shortly after birth, but the duration of the reaction varied. As was also noted by Salmon and Richman,<sup>5</sup> there appeared to be little correlation to jaundice or to the general condition of the patient. The triplets (patients 1, 2, and 3) gave similar reactions during the time all were living. The two that survived became negative

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TABLE I. CEPHALIN-CHOLESTEROL FLOCCULATION IN PREMATURE INFANTS

PATIENT	AGE	WEIGHT (GM.)	ICTERUS	CEPHALIN FLOCCULATION		COMMENT
				24 HR.	48 HR.	
1.	30 hr.	1,260	0	±	+++	One of triplets
	6 days	1,440	0	+	+++	
	13 days	1,463	+	0	±	
2.	30 hr.	1,305	0	÷	+++	One of triplets
	6 days	1,215	0	÷	+++	
	13 days	1,100	÷	0	0	
3.	30 hr.	1,500	0	+	+++	A triplet, died third day
4.	12 hr.	1,620	0	÷÷	+++	
	6 days	1,440	÷	++	+++	
	11 days	1,575	0	0	+	
	15 days	1,688	0	0	0	
5.	2 days	2,340	0	++	++++	Died at eight days
	7 days	2,205	+	++	+++	
6.	2 days	1,013	0	++	++++	
	6 days	945	++	++	++++	
	10 days	945	++	0	0	
7.	2 days	1,660	0	0	++	
	7 days	1,635	++	0	++	
	11 days	1,635	++	0	++	
	16 days	1,744	+	0	0	
8.	2 days	1,688	0	÷	+++	Diarrhea present
	11 days	1,603	÷	0	+++	Plasma given intravenously
	15 days	1,603	0	0	+++	
	19 days	1,631	0	+	+++	

at about the same time. Only one premature infant (patient 8) had a positive test after the second week, and this patient received several injections of human plasma for treatment of diarrhea.

Moore and associates<sup>6</sup> stated that in disease, a positive flocculation may be obtained with a serum due to any of the following alterations: (1) increase of gamma globulin in such quantity that there is insufficiency of the normal components of the serum albumin fraction to inhibit the reaction; (2) diminution of the serum albumin fraction below initial levels necessary to inhibit the reaction; (3) diminution in the flocculation inhibiting properties of the albumin fraction. There are many alterations in the newborn infant's blood which are peculiar to this period of life, and one of these is the high titer of antibodies carried over from the maternal circulation. Since the gamma globulin fraction represents some of these antibodies, the globulin fraction is increased. Whether this is adequate to explain the positive flocculation can be proved only by accurate determination of the gamma globulin and albumin in the infant at the time the flocculation is performed. This also should be obtained in the mother, since it has been found that her flocculation is positive during the same period of time as that of the infant.

As suggested above, gamma globulin and albumin fractions present in the patient's serum probably influence the degree of flocculation. The gamma globulin appears to produce positive results, while the albumin has an inhibitory effect. Recently, gamma globulin for the prevention of measles has become



TABLE II. CEPHALIN-CHOLESTEROL FLOCCULATION AFTER GAMMA GLOBULIN

PATIENT	AGE (YR.)	WEIGHT (KG.)	DIAGNOSIS	CEPHALIN FLOCCULATION BEFORE GAMMA GLOBULIN		GAMMA GLOBULIN INTRAMUSCULAR		CEPHALIN FLOCCULATION						GLOBULIN REQUIRED IN VITRO
				24 HR.	48 HR.	TOTAL	C.C./KG.	1ST DAY		2ND DAY		3RD DAY		
								24 HR.	48 HR.	24 HR.	48 HR.	24 HR.	48 HR.	
1.	10	35	Scarlet fever	0	0	20 c.c.	0.57			++	++	0	++	1:250
2.	8	26	Scarlet fever	0	0	20 c.c.	0.75					+	++	1:250
3.	1	5	Hirschsprung	0	0	2.1 c.c.	0.42	++	++			0	++	1:200
4.	1	6.8	Encephalitis	0	0	3.0 c.c.	0.44	++	+++					1:300
5.	1	9	Diarrhea	0	0	2.0 c.c.	0.22	0	++			0		1:300
6.	2	12.5	Pneumonia	0	0	2.0 c.c.	0.15	0	0					1:800
7.	2	13.5	Impetigo	0	0	3.0 c.c.	0.22	0	0					1:800
8.	1	6	Diarrhea	+	+	2.6 c.c.	0.44	+	++					1:800
9.	7	23	Pharyngitis	0	+	5.0 c.c.	0.22	0	++				++	1:1000
10.	11	27	Pneumonia	0	0	5.0 c.c.	0.18	++	+++				+++	1:1000

widely used. The idea was conceived that large dosages of this preparation might influence the outcome of the cephalin-cholesterol flocculation. To see if this were true, ten patients were given gamma globulin intramuscularly, and blood was removed from the patient twenty-four and forty-eight hours later. At the same time, a dilution of the gamma globulin preparation used in each case was tested to find the lowest concentration necessary to produce a positive test in vitro. This was found to vary markedly with the product. The first five patients received Armour's immune globulin and the remaining patients received Cutter's\* immune globulin. When 0.2 c.c. of the diluted material was used, it was found that dilutions of Armour's globulin below 1:300 was necessary, while the Cutter's globulin was active in vitro in 1:800 to 1:1000 dilutions. It was soon noted that different preparations of the cephalin-cholesterol water suspension varied in their sensitivity, and a control of distilled water and a known positive serum was necessary to evaluate the experiment. The procedure was performed in the same manner as described above for the premature infants, with the exception that the blood was usually obtained from the antecubital fossa.

As can be seen in Table II, the majority of the patients had a positive flocculation after the administration of the globulin intramuscularly. Three (patients 1, 2, and 5) continued to give these findings for at least seventy-two hours. Three others (patients 6, 7, and 8) showed no changes, although the globulin used was very active in vitro. The last (patient 10) had a 4+ reaction after receiving less of the same preparation. From these findings it appears that to evaluate properly a positive flocculation of a child, information should be obtained as to whether or not the patient may have recently received an injection of immune globulin.

#### SUMMARY

1. The cephalin-cholesterol flocculation is positive in premature infants during the first week of life, and often throughout the second.
2. The cephalin-cholesterol flocculation appears to be influenced when large amounts of immune globulin are given intramuscularly.
3. The cephalin-cholesterol flocculation is subject to many variable factors capable of producing false positive results.

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\*Immune Serum Globulin (Human) provided by the American Red Cross.

# MEASURING THE SPECIFIC GRAVITY OF SMALL AMOUNTS OF URINE

## A RAPID AND SIMPLE METHOD

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IT IS not unusual in pediatric practice to see the specific gravity determination omitted from the report of a urinalysis on young infants, due to the insufficient quantity of the specimen. Indeed it may at times be difficult or at least inconvenient to collect urine specimens of sufficient volume from tiny babies to permit a specific gravity determination by the clinical urinometer, notwithstanding the fact that this is an essential part of the laboratory investigation, particularly in disorders of the kidney or water metabolism.

The method described here makes it possible with a few drops of urine to determine the specific gravity in a few minutes.\*

### THE METHOD

Drops of urine are allowed to fall into a graded series of oily solutions made up by mixing kerosene and bromobenzene in varying proportions, ranging in specific gravity from 1.000 to 1.060. Note is made in each instance whether the urine drop rises or sinks in the given test solution, in a manner similar to that used in determining blood specific gravities with copper sulfate solutions.<sup>1</sup>

A series of sixteen test mixtures are graded from 1.000 to 1.030 at intervals of 0.002, and eight test mixtures ranging from 1.032 to 1.060 at intervals of 0.004. For the urine, a medicine dropper with a fine capillary tip is used, or a 20 c.mm. hemoglobin pipette, if the quantity of urine is too small. The tip of the pipette is brought about 3 cm. below the surface of the test solution, or to a point slightly above the center of the bottle, and a drop is gently forced out. If the drop is of the same specific gravity as the test mixture, it will tend to remain stationary in the solution; if heavier, it will sink to the bottom of the bottle; and if lighter, it will rise to the surface. According to the result in the first test bottle, others are selected until the value of the unknown has been bracketed by adjacent test solutions or one has been found in which it remains stationary. Thus, the specific gravity can be determined within 0.001 if the unknown is at 1.032 or less, and with 0.002 if denser than 1.032. It is advisable to make the initial trial with the 1.020 bottle and then proceed to 1.030 or 1.010 as indicated.

Although designed for use with small amounts of urine, this method may be employed for determining the specific gravity of other fluids as well.

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\*The gradient cylinder method of Linderström-Lang<sup>2</sup> may be used for urine. The present method has the following advantages: the plotting of curves is eliminated; the solutions can be carried about and shaken without ill effect; and the method can be used by any student without technical difficulty.

## PREPARATION OF STANDARD SOLUTIONS

Two stock solutions are first prepared, one of 952 ml. with a specific gravity of 1.000 and the other of 668 ml. with a specific gravity of 1.060. It is difficult to give precise figures as to the proportions of kerosene and bromobenzene in these stock solutions, due to the inconstancy in specific gravity of different stocks of the former. However, a kerosene-bromobenzene ratio of 70:30 yields a specific gravity of about 1.000, and one of 62:38 will be approximately 1.060. Solutions of these proportions can be adjusted to exact value by any of three methods:

1. By pycnometry.
2. By the addition of drops of aqueous solutions of known specific gravity, noting whether they rise or fall. For the stock solution of specific gravity 1.000, distilled water may be used as a test substance; for that of 1.060, a solution of 9.850 Gm. copper sulfate ( $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ ) in 100 ml. of water at  $18^\circ \text{C}.$  will be adequate.\*

3. By use of a certified clinical urinometer which has been tested for accuracy on solutions of known specific gravity.

After the two stock solutions are ready, they may be mixed in different proportions as shown in Table I. The stock solutions may be put in two burettes for convenience and delivered directly into the containing bottles, which should be equipped with tightly-fitting screw caps to prevent evaporation and leakage. It will be noted in Table I that to obtain a standard solution of a given specific gravity, the last two figures of the specific gravity give the number of milliliters of stock solution B to be diluted to 60 ml. with stock solution A; e.g., to make a solution of specific gravity 1.024, dilute 24 ml. of stock solution B with 36 ml. of stock solution A.

After preparing the twenty-four standard mixtures, it is desirable to check at least several of them by one of the three methods mentioned above.

Since it is recommended that initial trials with unknowns be made with the 1.020, 1.010, and 1.030 bottles, these standards will receive considerably more use than the rest and therefore it is advisable to make them up in extra supply.

## USEFUL LIFE OF THE STANDARD SOLUTIONS

Since both the organic and inorganic constituents of urine are practically insoluble in the test mixtures, the specific gravities of the latter have been found so far to remain nearly constant at a given temperature, even after the addition of 80 drops of urine to 60 ml. of test mixture, and over a period of several weeks. However, for mechanical reasons it will probably be found desirable to clear the bottles after the accumulation of this amount of urine.

After the bottles have been shaken, all urine drops will be either at the bottom or the top of the bottle, because by intermingling they will have arrived at a more or less homogenous specific gravity and will separate out from the organic solutions. Urine which has floated to the top may be pipetted off. That

\*If in the same laboratory the copper sulfate method for blood and serum specific gravities is in use, it will be found convenient to check both these stock solutions and the subsequently-prepared standard solutions by use of appropriate copper sulfate standards.

which has sunk to the bottom may most advantageously be removed with a separatory funnel; specifically, an ordinary burette may be used for this function. Filtering is another convenient and satisfactory way of clearing the standard solutions.

Notwithstanding the above, after the lapse of eight to ten weeks of use it may be a desirable precaution to test the mixtures by one of the methods mentioned elsewhere and to adjust them if necessary by the addition of drops of kerosene or bromobenzene.

TABLE I. MILLILETERS OF STOCK SOLUTIONS OF GRAVITIES 1.000 AND 1.060 TO BE MIXED TO PREPARE 60 ML. OF STANDARD TEST SOLUTIONS OF GRAVITY G\*

NO.	G	A	B	NO.	G	A	B
1	1.000	60	—	13	1.024	36	24
2	1.002	58	2	14	1.026	34	26
3	1.004	56	4	15	1.028	32	28
4	1.006	54	6	16	1.030	30	30
5	1.008	52	8	17	1.032	28	32
6	1.010	50	10	18	1.036	24	36
7	1.012	48	12	19	1.040	20	40
8	1.014	46	14	20	1.044	16	44
9	1.016	44	16	21	1.048	12	48
10	1.018	42	18	22	1.052	8	52
11	1.020	40	20	23	1.056	4	56
12	1.022	38	22	24	1.060	—	60

G, Gravity of standard test solutions.

A, Stock solution of specific gravity 1.000.

B, Stock solution of specific gravity 1.060.

\*A total of 932 ml. of A and 668 ml. of B needed for the entire set, numbers 6, 11, and 16 being prepared in duplicate as recommended.

#### THE EFFECT OF TEMPERATURE

The difference in coefficient of expansion between urine and those of the standard solutions is such as to introduce an error of 0.002 to 0.003 in the temperature range from 14° C. to 30° C. if the standard solutions are prepared at 22° C. However, it has been repeatedly shown that with ordinary urinometers much wider discrepancies are found with changes in temperature,<sup>3</sup> and different urinometers sometimes give widely different specific gravity readings.<sup>4</sup> It is felt, therefore, that the present method is of satisfactory accuracy for clinical use.

#### PRECAUTIONS

1. At least once a day the standard bottles should be shaken or inverted once or twice. This should be done before using if they have not been agitated for more than twenty-four hours. However, they must be allowed to stand for three to four minutes for gross currents to have subsided before drops of urine are introduced.

2. Occasionally, a drop of urine will not readily detach itself from the pipette. It may then be of help to move the pipette rapidly back and forth in a horizontal direction.

3. It is preferable to use small drops of urine for the reason that they permit more tests before the standard solutions need be cleared.

## SUMMARY

A simple method has been described, for determining the specific gravity of urine with a few drops of specimen, and of satisfactory accuracy for clinical use.

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## ADDENDUM

After submission of this paper, the writer's attention was called to a similar method published recently by Monroe and Hopper, using xylene instead of kerosene (*J. Lab. and Clin. Med.* 31: S, p. 934). It is felt that the method herein described has certain advantages over theirs. In the first place, the present method allows a much larger margin of error in the preparation of standards, viz: An increment in specific gravity of 0.001 is produced in their method by a difference of only 0.16 ml. of stock solution in a 100 ml. standard, whereas in using stock solutions described in this paper such an increment requires one millimeter in 60 ml. of standard. Thus their standards differ consecutively in specific gravity by 0.005, whereas in the present method by only 0.002, permitting a greater accuracy in results. Secondly, kerosene is considerably cheaper and more readily available than xylene.

# RELATIONSHIP OF WEIGHT AND LENGTH OF INFANTS AT BIRTH TO THE AGE AT WHICH THEY BEGIN TO WALK ALONE

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THE contention that heavier children are likely to learn to walk later than lighter ones is more than a mere popular belief, although little scientific evidence which supports that conclusion has been recorded. Shirley,<sup>1</sup> who observed twenty-five babies during their first two years of life, stated that the muscular and small-boned babies walk alone earlier than the short, rotund babies or the exceedingly heavy ones. She suggested that retardation in motor development of two or three of the children she observed may have been due to their large size. Peatman and Higgon<sup>2</sup> quoted Louttet, who stated that the age of walking was affected to some extent by the weight of the child. Strang<sup>3</sup> wrote that the slender, linear child walked at an earlier age than the broad, heavy child. Strang stated that girls tend to walk at an earlier age than boys. Terman<sup>4</sup> found that among 565 gifted children, the girls were more precocious than the boys in walking. Peatman and his associate found that among 349 normal infants, correlations were of zero order between the age at which the infants started to walk and the relative weight and indices of bodily build at the time. It seemed appropriate to find whether an objective and quantitative examination of available data would reveal any relationship between the age at which the children began to walk and their length and weight at birth.

The data utilized were obtained on 194 normal babies who were observed periodically from birth to the latter part of the second year. The weight and length at birth were noted to the nearest gram and centimeter, respectively, and converted to pounds and inches. The age at which the child walked alone was defined as the age when he began to take several steps alone. In most instances this date was obtained from the mother when she brought her infant for his monthly visits, and while this method may be subject to considerable inaccuracy if the history is obtained weeks or months later, it should be fairly definite when taken at such frequent checkup visits during the period at which the accomplishment occurs.

In the group of infants studied, ninety-nine were boys and ninety-five were girls. The mean age at which the male infant began to walk was  $11.97 \pm 0.16$  months, which does not differ statistically from the mean age of  $11.84 \pm 0.21$  months computed for the girls.

The weight of the infants at birth and the age at which they first walked alone showed a slightly inverse relationship. The correlation coefficient for these two variables was  $-0.09$ , which is not statistically significant. The random probability of getting a negative correlation as large as  $0.09$  in samples of this size is  $0.3$ ; only probability values equal to or less than  $0.05$  generally are considered to be statistically significant.

Contrary to expectation the babies who were longer at birth were found to have walked alone at an earlier average age than the shorter ones. The upper 25 per cent in order of length, that is, the forty-eight longest ones (mean length:  $20.7 \pm 0.07$  inches), started to walk when they were  $11.4 \pm 0.24$  months old, while the forty-eight shortest babies (mean length:  $18.7 \pm 0.05$  inches) started to walk when they were  $12.5 \pm 0.25$  months old. The difference in the age of walking alone of the longest and the shortest 25 per cent of the series is a little more than one month. The correlation coefficient for these two variables was  $-0.27$ . Since the probability of getting a negative correlation as large as  $0.27$  in this sample is  $0.04$ , this relationship may be considered statistically significant. The linear equation for prediction of age at which a child will begin to walk from length alone was

$$\text{Age} = 21.97 - 0.51 L$$

in which age is given in months and  $L$  represents length at birth in inches. It is to be noted that the original data in respect to age at which the child first walked alone were obtained during interviews with the mother and were not observed directly. Any inaccuracy in this will be reflected in a lower apparent correlation as obtained from the calculations. Therefore it may be said that with more precise data in these records it is likely that a somewhat greater, but still small, correlation with length would have been found. Consequently, it is indicated that length is a factor, but by itself is only a relatively unimportant one, in determining the age at which an infant will begin to walk.

Next, the age at which the child started walking was investigated in relation to the weight and length at birth taken together. The partial correlation of age at which the child began to walk alone with length, for constant weight, was  $-0.29$ . The partial correlation of age at which the child began to walk alone with weight, for constant length, was  $+0.13$ . The multiple correlation coefficient for both variables together was  $0.30$  ( $P = 0.03$ , statistically significant). The linear equation for predicting age at which a child will walk alone from length and weight together was found to be

$$\text{Age} = 24.33 - 0.73 L + 0.26 W$$

in which  $W$  represents weight of the child at birth in pounds. In studying the partial correlations and the equation in terms of length and weight, an attempt was made to determine the relationship of age at which the child begins to walk alone, on the one hand, with length of babies all of the same weight at birth and on the other hand, with weight for babies all of the same length at birth. Equation 2 indicates that for infants of any given weight, an increase of an inch in length decreases the average age at which the baby starts walking by about twenty-two days. For infants of any given length, on the other hand, an increase of a pound in weight at birth increases the age at which the child begins to walk, on the average, by about eight days. Thus, it is apparent that infants who are longer for their weight walk at an earlier age than those who



are relatively short for their weight, corroborating the opinion of Strang previously mentioned that children of the linear type of build walk alone at an earlier age.

The relationship of the age at which a child begins to walk to weight and length was investigated also by relating age to the index  $W/L^3$ . The correlation found with this index was +0.20, indicating again that the babies who are heavier for their length begin to walk later, but the correlation was brought out more definitely by use of the linear equation ( $R = 0.30$ ), than by the index  $W/L^3$ .

#### SUMMARY AND COMMENT

The relationship of the age at which 194 babies began to walk alone to their length and weight at birth was investigated. Ninety-nine of the babies were boys and ninety-five were girls. The average age at which girls began to walk alone was only slightly earlier ( $11.84 \pm 0.21$  months) than that at which boys began to walk alone ( $11.97 \pm 0.16$  months). However, when the size of the group investigated is considered, this difference is not statistically significant. No significant correlation was found between age at which the babies started walking and weight at birth considered by itself.

The length at birth was found to be correlated negatively with age at which the babies began to walk ( $r_{AL} = -0.27$ ). An increase of an inch in length was associated with a decrease of an average of about fifteen days in the age at which the child began to walk.

The greatest correlation found was when length and weight were considered together ( $R = 0.30$ ). For babies all of the same weight, an increase of an inch in length was associated with a decrease of an average of twenty-two days in the age at which the child began to walk and for infants of the same length, an increase of a pound in weight at birth was associated with an increase of an average of eight days in age of walking alone. The infants who were relatively long for their weight, therefore, began to walk at an earlier age than the others.

In view of the rather small number of cases included in the study, the results cannot be considered definitive until corroborated with observations in a larger number of cases.

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# Case Reports

## ATRESIA OF THE ILEUM

### FIRST SUCCESSFUL CASE CURED BY ENTEROSTOMY ALONE

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HONOLULU, T. H.

**A**TRESIA of the intestinal tract is, fortunately, a rare condition, appearing about once in 20,000 babies, according to Farr and Brunkow.<sup>1</sup> The condition was first described by Calder<sup>2</sup> of Edinburgh in 1733, in the *Medical News* under the title, "Two Examples of Children Born With Preternatural Conformation of the Guts."

Numerous theories have been advanced for the etiology of this condition. In 1889, Sutton<sup>3</sup> wrote, "Congenital obstructions and narrowing of the alimentary canal are always found in the situation of embryologic events. Imperforate ileum occurs in the region where the primitive alimentary canal is in communication with the yolk-sac by means of the vitelline duct." The most plausible explanation seems to be that atresia results from an arrest of development in the embryo when, for some unknown reason, the intestinal tube fails to clear itself of the epithelial concrescences. This process is well illustrated by the accompanying pictures (Figs. 1 and 2) from *Abdominal Surgery of Infancy and Childhood* by Drs. Ladd and Gross.<sup>4</sup>

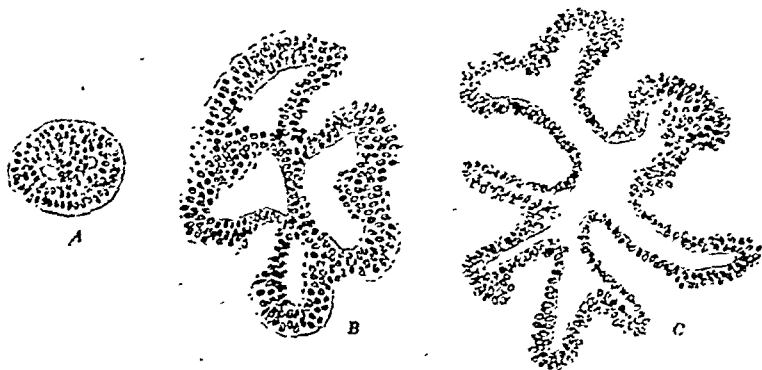


Fig. 1.—A, Concrecence of intestinal epithelium after five weeks of fetal life; B, showing formation of cystic spaces; C, intestinal lumen cleared by twelfth week. (From Ladd and Gross after Kelbal and Mall.)

The site of the atresia may be anywhere in the intestinal tract, although the colon is rarely involved. In 1922, Davis and Poynter<sup>5</sup> collected 392 cases, in which 101 were located in the ileum and colon. Less than one-third of these reported cases were subjected to laparotomy. Ladd and Gross,<sup>4</sup> in 1941, stated that in fifty-two cases of atresia, thirty-four were located in the ileum.

In 1889, Sutton<sup>3</sup> correctly diagnosed what he called "imperforate ileum" and performed an enterostomy. The atresia was eighteen inches from the ileocecal valve. "The child rallied and took food, but about six hours later it

From the surgical department of Queen's Hospital.

suddenly expired." Sutton<sup>3</sup> concluded that this was the first case of atresia diagnosed during life and operated upon. He was evidently unaware that Von Tischendorf<sup>6</sup> had reported a patient with enterostomy on the seventh day who survived for fifteen days.

No baby born with intestinal atresia lived until the year 1911, when Fockens<sup>7</sup> of Rotterdam reported a case of atresia of the ileum successfully cured by lateral anastomosis. Ten years later Demmer<sup>8</sup> of Vienna reported a cure by the same method. In 1933, Carter<sup>9</sup> had a successful outcome following lateral anastomosis between ileum and descending colon plus ileostomy. Ladd and Gross<sup>4</sup> report three successful cases of atresia of the ileum cured by primary anastomosis.

In 1931, Webb and Wangenstein<sup>10</sup> published a thorough but lugubrious article, reporting fifteen fatal cases of atresia of the intestinal tract, of which six patients were submitted to operation and the diagnoses of the remaining nine were confirmed at autopsy. The authors concluded that "anastomotic procedure is the only operation that holds any promise of success. The establishment of a complete external intestinal fistula in the infant is doomed to failure from the start. No instance of recovery following enterostomy has occurred."



Fig. 2.—Typical x-ray findings.

In 1939, Miller<sup>11</sup> wrote: "There has never been a successful result recorded where ileostomy alone has been used. A short circuiting lateral anastomosis offers the only hope of success." Ladd and Gross<sup>4</sup> (1941), as the result of their extensive surgical experience, conclude that "ileostomy is a poor surgical procedure. To our knowledge there has been no case in the literature which has been successful with enterostomy alone."

It is perhaps fortunate that the author had not seen the articles quoted before April 28, 1946, when he was called to operate on a 3-day-old Chinese baby with atresia of the ileum. As the baby made a complete recovery with ileostomy alone, the case is reported in considerable detail.

A Chinese female, a second child, was born by a normal delivery with a birth weight of 7 lbs., 14 oz. Vomiting started after the first feeding. The baby had several bowel movements. Nothing unusual was noted as to the meconium. Farber's<sup>12</sup> test (absence of cornified epithelium in the meconium) was not done, as we were not acquainted with the test. Abdominal distention appeared soon and developed to a marked degree. Bile-tinged vomiting continued. No visible peristalsis was observed. The veins of the abdominal wall were distended. There were a few peristaltic sounds heard with the stethoscope. Dehydration was marked. There was slight fever. X-ray findings were typical of small intestinal obstruction with fluid level.

The preoperative diagnosis was obstruction of small intestine.

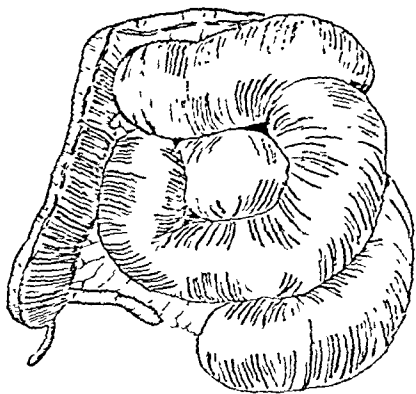


Fig. 3.

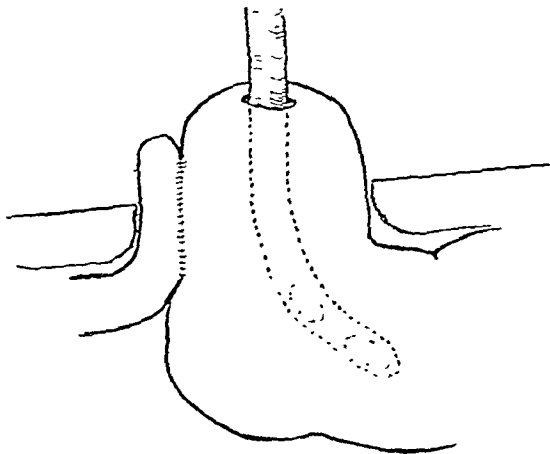


Fig. 4.

Fig. 3.—Diagram of operative findings. Proximal loop greatly thinned out and distended. Distal segment and colon contracted. Gap of 2 inches between rounded ends.

Fig. 4.—Operative procedure on third day. First stage.

**First Operation.**—April 28, 1946. After lavage of the stomach and administration of parenteral fluids, under drop ether anesthesia a laparotomy was performed through a right rectus incision. Considerable clear, peritoneal fluid was evacuated and the atresia was found without difficulty in the lower ileum about 3 inches from the ileocecal valve. There was a gap of 2 inches between the two rounded ends of the segments. The proximal bowel was extremely distended about 4 cm. in diameter and the wall was thinned out. The distal segment was the size of a cigarette. There was a V-shaped gap in the mesentery and there was no fibrous strand connecting the two rounded intestinal ends. The colon was contracted to the size of an adult index finger. The two segments were sutured together with fine cotton and exteriorized. The gap in the mesentery was closed. A No. 12 catheter was inserted into the proximal bowel and the abdominal wall was partly closed without suturing the intestine to the peritoneum. Thin, brownish material drained at once per catheter, the distention subsided, and after recovery from the anesthetic, the baby ceased vomiting. Inhalations of oxygen were given with apparent benefit and a Wangenstein tube was inserted.

**Second Operation.**—May 2 (no anesthetic). The catheter was removed. The ends of the protruding intestine were incised. The distal segment had dilated to an amazing degree. The septum was incised for about an inch and the intestinal walls were sutured with fine chromic gut. A small Kocher clamp was applied to the balance of the spur. This procedure was undertaken in order

to provide the possibility of some intestinal contents passing at once from the proximal to the distal loop. In forty-eight hours the baby had a movement by rectum. The clamp was tightened every day and cut through on the fourth day. A finger, inserted in the stoma, showed a large communication between the two loops, the calibre of which was greater than the intestinal calibre. As recommended by Ladd and Gross,<sup>4</sup> enemas of saline solution were given twice

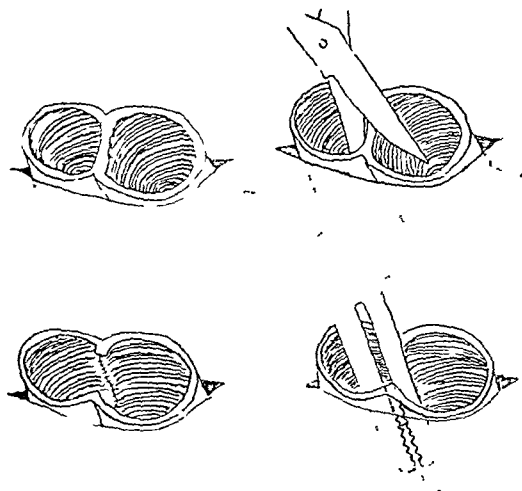


Fig. 5.—Operative procedure four days later. Incision of septum and suture of intestinal wall and small Kocher clamp applied to lower part of spur.

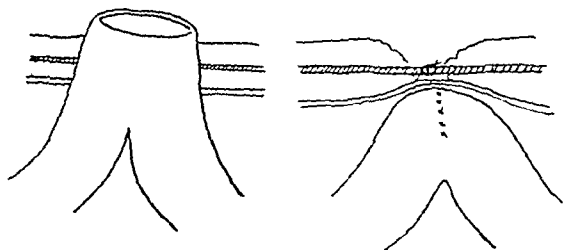


Fig. 6—Ileostomy open for eighty-three days Closure of same.

a day in order to distend the colon. The feces were discharged about half by the stoma and half by rectum. There was a surprising amount of fluid loss from the enterostomy. The surrounding skin became excoriated. Starch powder applied liberally was found effective in counteracting the irritation. As the protruding intestinal ends began to slough, there were several small hemorrhages which were readily controlled by sutures. The baby held her own and began to gain weight. The plan then was to close the enterostomy when it had contracted and when the major part of the feces was being passed by rectum. This procedure was based on the practice adopted in surgery of adults, usually a six-week to two-month period being allowed for the intestinal stoma to contract. In a crying baby conditions are different. The stoma refused to contract, natural bowel movements became less and less and finally ceased and when the baby cried, the lowest part of the stoma began to prolapse.

*Third Operation.*—July 9 (drop ether anesthesia). This consisted of an attempt at closure of the enterostomy by the method usually used in surgery

of adults. This operation was an ignominious failure. The wound held for eight days and then broke down and conditions were as before.

*Fourth Operation.*—July 24 (drop ether anesthesia). The bowel was freed at the mucocutaneous junction, the edges pared and sutured with Connell cotton stitches. The skin margins were dissected back and strands of fascia and atrophic muscle were carefully sutured over the intestinal wound with fine steel wire. A light petrolatum gauze pack was placed in the wound and the skin edges were left open. A rubber pad was held on the wound by a spica ace bandage. There was a considerable discharge from the wound of a thin, watery fluid for a few days but no fecal matter. The wound healed solidly and the baby was discharged August 21 in good condition, weighing 10 lbs., 1 oz.



Fig. 7.—Baby on discharge from hospital, 118 days old (weight, 10 lb., 9 oz., birth weight, 7 lb., 14 oz.), showing healed wound.

*Supplementary Therapy.*—During her stay in the hospital, the baby received thirteen whole blood transfusions, given into the scalp veins by the pediatricians. The amazing loss of fluids from the stoma was vigorously combatted by hypodermoclyses, forty-seven in all. Water and electrolytes were supplied by Lactate-Ringer solution and glucose; plasma and vitamins were given according to indications. Penicillin was administered in eighty-three doses of 10,000 units each. Some sulfadiazine was given and a course of sulfasuxidine for five days before the last operation. The baby was fed breast milk at first and then was put on a formula with iron and vitamins added to the mixture.

#### COMMENTS

1. A report is made of a case of atresia of the lower ileum cured by enterostomy alone. According to the literature, this is the first cure recorded by this method.

2. It should be distinctly understood that a successful outcome by ileostomy alone can only be expected when the atresia is located low in the ileum. An atresia higher up in the ileum or in the jejunum must be treated by a primary anastomosis.

3. An ileo-ileostomy in a newly born baby is a time-consuming and delicate operation with a high mortality. In case the atresia is low down in the ileum, the question arises whether an ileostomy with early division of the spur is not a wiser procedure.



Fig. 8.—X-ray taken September 6, showing steel wire in abdominal wall and normal colon.

4. This report shows that a baby can survive with enterostomy alone provided the atresia is in the lower ileum. The dehydration and malnutrition must be combatted vigorously. Nowhere in the field of medicine is teamwork between physician and surgeon more important than in a condition of this kind, where nutrition means everything.

5. In retrospect, at least two mistakes were made. Following the practice in surgery of adults, we expected the stoma to contract and waited in vain for this to occur. The closure of the stoma should be done when the mucocutaneous junction is well formed, perhaps between the third and fifth week. The second mistake was in the method of suture. In the operation that failed, the bowel wall was freed and sutured and through-and-through silk stitches brought the abdominal wall together. By this method the sutured intestinal line does not receive sufficient support to counteract the explosive effect of the baby's cries. Also, the skin should not be sutured. Steel wire made an admirable suture material.

My thanks are due to the pediatricians, Drs. D. C. Marshall, F. D. Nance, and C. M. Florine, to the devoted and efficient Japanese nurses, to Drs. R. G. Hunter and K. B. Conger for their able assistance, and to Dr. Conger for the drawings.

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# SEXUAL PRECOCITY AND ACCELERATED GROWTH IN A CHILD WITH A FOLLICULAR CYST OF THE OVARY

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**P**REMATURE development of the genital organs associated with an increase of body size may be due to various causes. These can be conveniently classified into three groups:

1. Those due to endocrine disorders such as hyperplasia or neoplasms of testicular, ovarian, or cortico-adrenal cells.

2. Those due to changes in the central nervous system, consisting chiefly of intracranial tumors. These are usually located near the floor of the third ventricle and presumably have an irritating or stimulating effect on the anterior pituitary gland, which in turn stimulates the gonads.

3. A poorly defined group in which no lesion can be found, a so-called constitutional group.

There is also a syndrome, first described by Albright<sup>1</sup> in 1937, the etiology of which is as yet unknown, but which has been suspected as being due to some disturbance in the central nervous system. This syndrome consists of disseminated fibrosis of bone, extensive patchy areas of cutaneous pigmentation, precocious growth, and, among females, precocious sexual development.

In young females with precocious sexual development there is usually hypertrophy of the breasts, uterus, and labia, and often the appearance of pubic and axillary hair. Frequently there is uterine bleeding, or precocious menstrual periods, and in some cases a marked increase in body size. In some of these patients, even very young girls, pregnancy is possible. However, according to Novak,<sup>2</sup> this possibility exists only among those of the constitutional type.

The urinary excretion of estrogens has been found to be markedly elevated in most patients with granulosa cell tumor of the ovary as well as in some of those with hyperplasia or tumor of the cortico-adrenal cells. In those with cortico-adrenal tumors, however, an increase in the urinary excretion of alpha and beta 17-ketosteroids is also found, while no such increase is present in those with granulosa cell tumor of the ovary.

The number of reported cases of ovarian tumors associated with precocious sexual development among children is small. Lull,<sup>3</sup> in a review of the literature published in 1941, was able to collect only sixteen reported cases in which granulosa cell tumor of the ovary was responsible for premature sexual development. He added one case, that of a 9-month-old infant, the youngest so far reported. He also reported, in the same article, a case of premature sexual development in a 22-month-old girl. A granulosa cell tumor was suspected, but at operation she was found to have a follicular cyst of the ovary. This child's symptoms regressed and the sexual development reverted to the infantile type following surgical removal of the cyst. Quantitative examination of this child's urine preoperatively showed the absence of any measureable amount of estrogen.

Fischer,<sup>4</sup> in 1940, reported the case of a 4-year-old girl with the characteristic changes of sexual precocity, including periodic vaginal bleeding for eight months, enlarged breasts, nipples, labia, and increased height. Quantitative urinary pregnanediol determinations preoperatively showed results comparable to those found in the early months of pregnancy (31 mg. of pregnanediol glucuronate). At operation the left ovary was removed and was found to contain many small cysts, the largest being 1.2 cm. in diameter. No evidence of granulosa cell tumor was found. Up to the time of publication of his case report,

five months after the operation, there had been no recurrence of the vaginal bleeding. However, no very marked decrease in size of the breasts, nipples, or labia had occurred up to that time. No mention was made regarding post-operative urinary hormonal studies. Fischer concluded that he preferred to assign his patient to the constitutional group rather than to attribute the precocious development to the cysts found in the ovary.



Fig. 1.—Appearance of the patient at time of first examination.

Additional observations over a longer period of time in Fischer's case would be of considerable interest. If this patient were of the constitutional type, the symptoms and changes in body development would be expected to continue despite removal of the cystic ovary. As stated previously, the vaginal bleeding had not recurred up to five months postoperatively. One wonders if this did recur later on and whether or not there was a subsequent return of the breasts and labia to normal size.

Except for the two previously mentioned cases reported by Lull and Fischer, no references in the literature were found similar to the case here reported, in which the precocious changes were associated with, and apparently caused by, a follicular cyst of the ovary.

## CASE REPORT

This case is that of a female, white child, 25 months of age. The family history is noncontributory and the past history is essentially negative.

The presenting complaint was vaginal bleeding, which first occurred on May 23, 1942. There was approximately one tablespoonful of blood present in the child's underclothing. A very slight mucoid vaginal discharge had been present for three days prior to the onset of bleeding.

Examination of the patient on May 23 showed a moderate but very definite hypertrophy of the breasts and nipples, with quite prominent pigmentation about the nipples. The labia minora were moderately enlarged. Abdominal examination revealed no apparent enlargement of the liver or spleen, and no masses could be felt in the kidney or adrenal regions. Combined rectoabdominal examination revealed a moderately enlarged uterus slightly to the left of the midline, but no definite mass was palpated in either adnexal region.

The child was very tall for her age, her height being  $39\frac{1}{2}$  inches, her weight  $31\frac{1}{2}$  pounds. According to the table of height curves prepared by Burgess,<sup>3</sup> the average height for girls of this age is  $34\frac{1}{2}$  inches while 99 per cent are less than 38 inches tall. This patient was 5 inches taller than the average and  $1\frac{1}{2}$  inches taller than the 99 per cent curve.

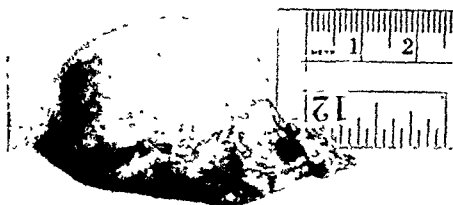


Fig. 2.—Surgical specimen showing appearance of right ovary and tube.

The vaginal bleeding lasted for two days. It did not recur.

It was quite evident that we were dealing with a case of sexual precocity with accelerated growth, but its cause was not yet clear. Four possibilities were considered: (1) constitutional type of sex precocity; (2) granulosa cell tumor of the ovary; (3) neoplasm in the region of the third ventricle of the brain; and (4) either hyperplasia or tumor of the cortico-adrenal cells.

Examination of the eyegrounds showed no abnormalities, the tendon reflexes were equal and normal, x-ray films of the skull were normal, and an intravenous urogram showed no abnormalities. Blood pressure was within normal limits. The urine examination was normal as was the hemoglobin, leucocyte count, and differential leucocyte count. A chest x-ray was negative. X-rays of the wrists showed normal bone development. Her mental development was normal. There were no pigmented areas of the skin, and x-rays of the long bones were normal. The tuberculin test was negative.

Quantitative determinations of urinary estrogen and ketosteroids were done by Dr. Leo Samuels. He reported finding a greatly increased amount of estrogen (30 I.U.). Doctor Samuels stated that this was as much estrogen as would be contained in the urine of a mature woman during the first week after menstruation. There was no abnormal increase in the urinary ketosteroids.

On the basis of these findings, a tentative diagnosis of granulosa cell tumor of the ovary was made, and operation was advised.

Dr. Irvine McQuarrie saw the patient in consultation at this time. His findings and conclusions coincided with those outlined.

On June 4, 1942, operation was performed by Dr. R. F. Hedin under open drop ether anesthesia. Upon opening the peritoneal cavity, the uterus was



Fig. 3.—Photomicrograph ( $\times 60$ ) of section through cyst wall.

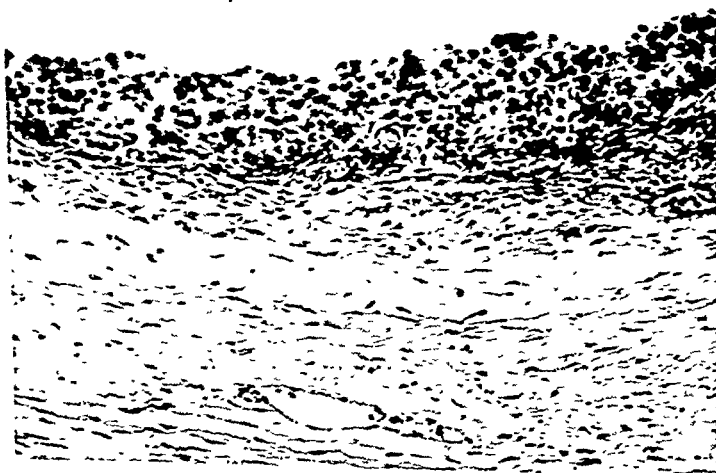


Fig. 4.—Photomicrograph ( $\times 200$ ). The dark-staining layer of cells is granulosa cells lining the cyst.

found to be moderately enlarged, and the left ovary appeared to be normal. The right ovary consisted chiefly of a cyst 4 by 3 cm. in diameter, which had destroyed most of the ovarian tissue. A right salpingo-oophorectomy was performed.

The entire specimen was sent intact to Dr. A. C. Broders, who was unable to find any evidence of a granulosa cell tumor. Drs. Robert Meyer and Malcolm Dockerty, who also saw the sections from this cyst, classified it as a follicular cyst of the ovary. It was Dr. Meyer's impression that sufficient estrogen to cause the changes noted in this patient might have been produced by the granulosa cells which lined the cyst.

One month following the operation, and again eighteen months later (January, 1944), quantitative determinations of urinary estrogen and ketosteroids were made by Dr. Samuels. All of these determinations showed normal values for both estrogens and ketosteroids.

Three months after the operation the breasts had decreased considerably in size. It has now been four years and four months since the cyst was removed. The patient has been seen several times during this period. There has been no recurrence of vaginal bleeding, and the labia, uterus, and breasts have regressed to normal size. There have been no additional complaints of any kind. Her height, however, remains proportionately as great as before. When last examined, on Sept. 6, 1946, her height was 51½ inches, her weight 53 pounds. This is about 6 inches above average height and 1½ inches taller than 99 per cent of girls her age.

#### SUMMARY

1. Sexual precocity with accelerated somatic growth due to ovarian tumors or cysts is relatively rare. Approximately twenty cases in young girls caused by granulosa cell tumors of the ovary have been reported.

2. A case of this character in a 25-month-old girl is reported. She had all of the changes one would expect to find in a case of granulosa cell tumor of the ovary, including a greatly increased urinary estrogen level. At operation, the right ovary was found to consist chiefly of a cyst 4 by 3 cm. in diameter. Following its surgical removal, careful search showed no evidence of a granulosa cell tumor. The cyst was classified as a follicular cyst of the ovary.

The patient has been observed for over four years since the operation. There has been no recurrence of vaginal bleeding. The breasts, nipples, and labia have regressed to their normal size. The estrogen content of the urine has decreased to a normal level and remained normal.

3. A search of the literature revealed only two previously reported cases similar in some respects to the case reported here.

Grateful acknowledgment is made to Dr. Irvine McQuarrie for his kindness in examining the patient and for his helpful suggestions, to Dr. John McKelvy for his interest in the case, to Dr. Leo Samuels who performed the urine assays, and to the pathologists who examined the specimen, Dr. A. C. Broders, Dr. Robert Meyer, and Dr. Malcolm Dockerty, who also prepared the photomicrographs.

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## CONGENITAL THROMBOCYTOPENIC PURPURA

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CONGENITAL thrombocytopenic purpura is a rare condition, but it does occur often enough so that it must be considered as a possible cause of bleeding tendencies in a newborn infant. There have been twenty cases previously reported, and it may be well to review briefly these previous reports before presenting our own cases. Sanford,<sup>1</sup> in 1936, reviewed the literature of twelve cases and presented the case of a female infant whose mother had also had purpura. Davidson,<sup>2</sup> in 1937, reported thrombocytopenic purpura in an infant whose mother had had a splenectomy for this condition. Whitney,<sup>3</sup> in 1942, and Urbanski,<sup>4</sup> in 1942, each presented reports of two consecutive children of mothers with purpura. Morrison,<sup>5</sup> in 1945, presented a single case, and Schefrin,<sup>6</sup> in 1945, reported thrombocytopenic purpura in an infant whose mother had never had any bleeding tendencies.

We have recently seen thrombocytopenic purpura occur in the neonatal period in three successive offspring of a mother with idiopathic thrombocytopenic purpura treated by splenectomy three years before the first pregnancy.

### CASE REPORTS

The mother of these children was first admitted to City Hospital on June 3, 1938, at the age of 17, with menorrhagia, bleeding gums, and petechiae. The red count at this time was 1,110,000; platelets, 1,105; bleeding time, 45 minutes; and clotting time normal, with no clot retraction. Idiopathic thrombocytopenic purpura was diagnosed, and a splenectomy was performed on June 30, 1938, with an uneventful convalescence. Following splenectomy the mother was not seen again until Jan. 17, 1941, when she was seven months pregnant. She had been asymptomatic until two months previously, but for the past two months had been having frequent nosebleeds. Examination at this time showed the platelet count to be 25,000, the bleeding time 30 minutes. She was followed in prenatal clinic for the next two months with weekly transfusions up to the time of delivery. During this time there was no appreciable change in the number of platelets but there was cessation of bleeding.

On March 1, 1941, a full-term female infant, D. H., was born (Chart 1). This baby appeared normal at birth, but six hours after birth petechiae appeared over the body; the platelet count was 8,500; liver and spleen were not palpable. On the fourth day of life, blood appeared in the stools and continued for the next week. On the baby's fifth day, the platelet count had dropped to zero, and it then began to rise spontaneously. Bleeding time was 30 minutes. There was no abnormal bleeding after the tenth day, although the baby received no transfusions until she was 3 weeks old; by this time the platelets had risen spontaneously to 20,000. During the next month she received five transfusions, and the platelets continued to increase, showing a precipitous rise at the age of 5 weeks. She was discharged on May 15, 1941, at the age of 2 months, with 542,000 platelets. For the next eighteen months she was followed in clinic, and during this time the blood picture remained normal.

The mother was next seen again in prenatal clinic on Jan. 30, 1945, six months pregnant; blood examination showed only three platelets per cubic

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millimeter, although there had been no spontaneous bleeding or petechiae. She was again followed in clinic with weekly transfusions throughout the remainder of pregnancy and at delivery had 64,000 platelets, with the bleeding time 15 minutes.

A second full-term female infant, C. H., was born on April 24, 1945 (Chart 2). The baby's platelet count immediately after birth was 5,000; six hours later this dropped to zero, bleeding from the cord appeared, and petechiae were noticed over the body. Liver and spleen was not palpable. On the

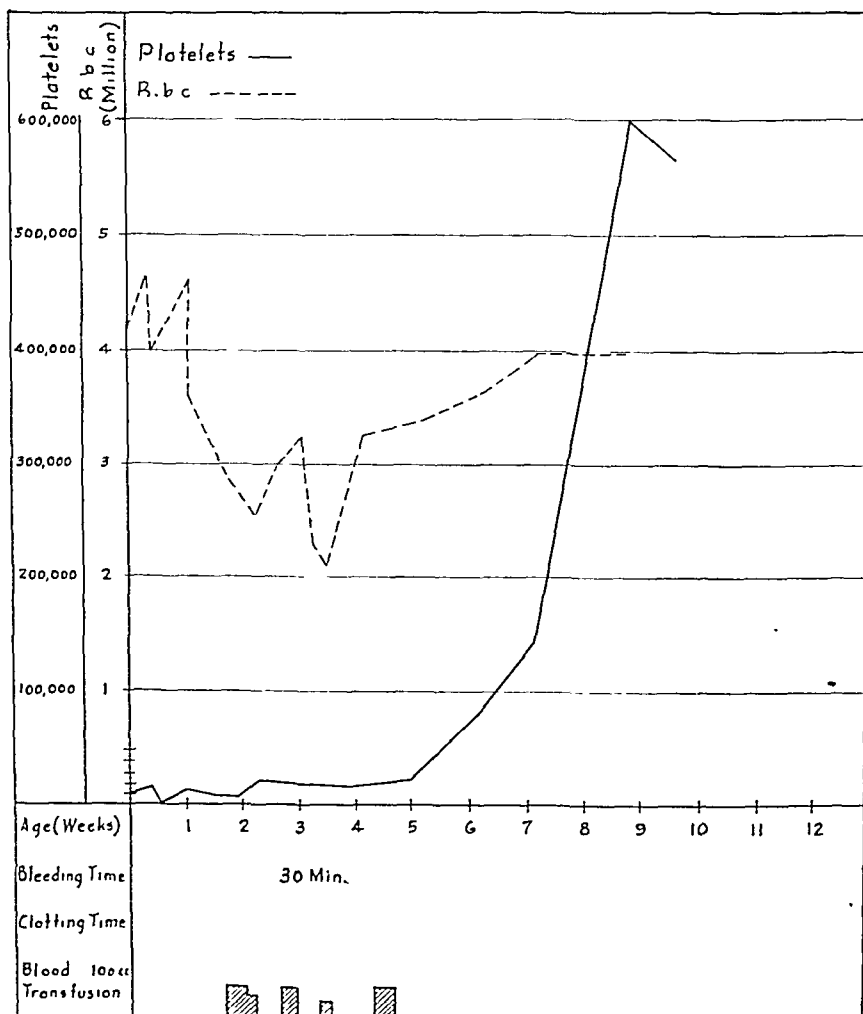


Chart 1.—D. H., March to May, 1941.

third day, blood appeared in the stools. At the age of one week, the platelet count remained at zero, bleeding time was 41 minutes, clotting time 15 minutes with no retraction, and blood was still present in the stools. During the second week the platelets began to increase spontaneously, the bleeding time decreased, and no more bleeding tendencies were apparent. No transfusions were given until the baby was 5 weeks old; by this time the platelet count had risen considerably,

and two transfusions were then given because of anemia. This baby was discharged on June 25, 1945, at the age of 2 months, with 981,000 platelets. She was followed in clinic for the next three months, during which time she remained asymptomatic with a normal platelet count, and was seen again at the age of 16 months with no bleeding tendencies and a normal blood picture.

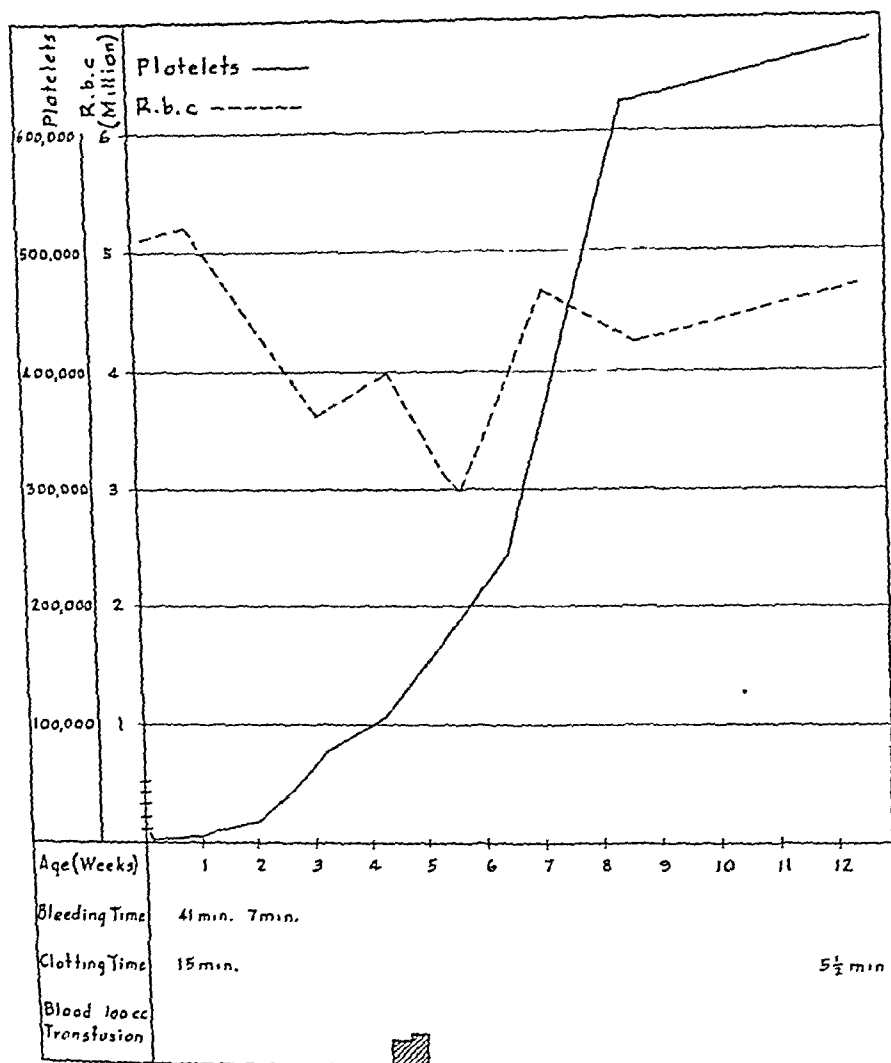


Chart 2.—C. H., April to July, 1945.

The mother's next admission to the hospital was on Aug. 20, 1946, with bleeding gums, petechiae, and 7,580 platelets. She had again been asymptomatic until the last half of pregnancy. A female infant, two weeks premature, was born on Aug. 21, 1946. Thorotrast study of the mother during this admission failed to reveal any accessory spleen.

This third child, S. H. (Chart 3), appeared normal at birth, but developed petechiae at the age of 2 days; platelet count was zero, bleeding time 62 minutes, clotting time 3 minutes, with no clot retraction; liver and spleen were not palpable. When the baby was one week old, the platelet count remained zero, the



bleeding time was still prolonged to 45 minutes with no clot retraction, and blood appeared in the stools. Tibial puncture, performed August 31, was followed by hematoma formation over the puncture site. The baby received transfusions every other day of life beginning on the second day, but there was no change in the number of platelets until she was 2 weeks old. From then on the platelets

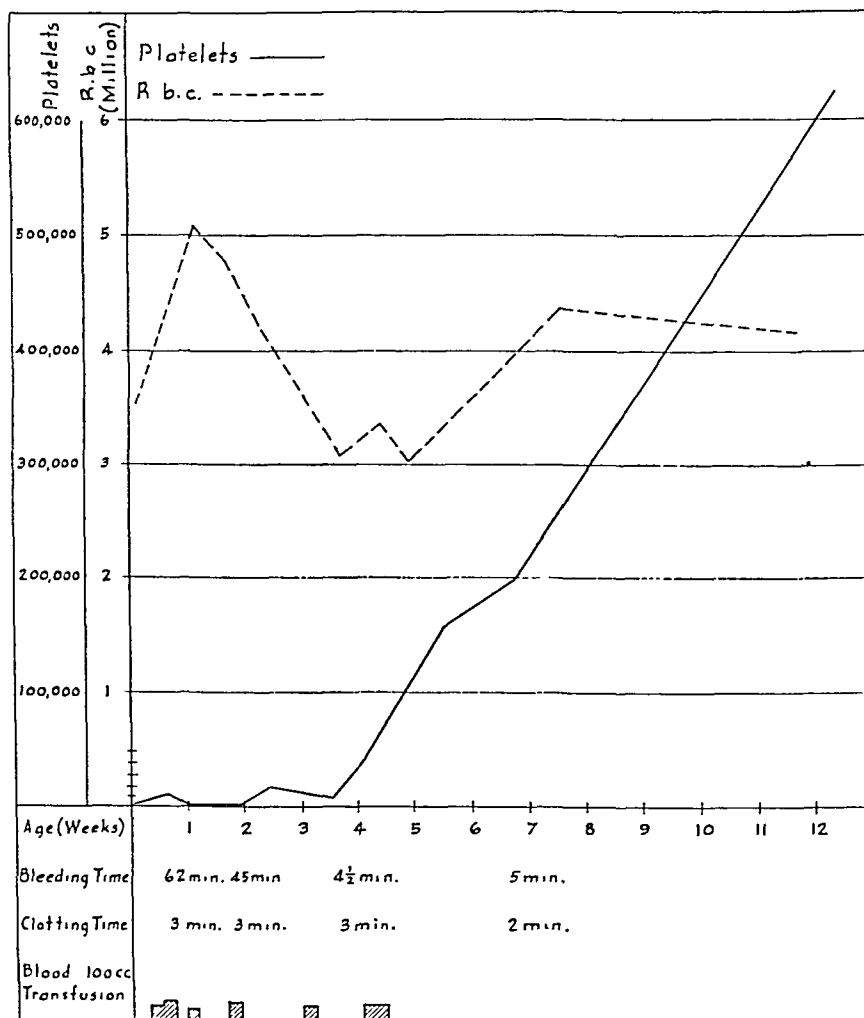


Chart 3.—S. H., August to November, 1946.

gradually increased, with diminishing bleeding time and disappearance of bleeding tendencies. She was discharged Oct. 17, 1946, at the age of 2 months, with 169,000 platelets, bleeding time 5 minutes, and clotting time 2 minutes, but still no clot retraction. On Nov. 12, 1946, she had 1,645,000 platelets, and there were no bleeding tendencies apparent.

#### SUMMARY

Congenital thrombocytopenic purpura has occurred as a familial condition in three successive children of a mother previously splenectomized for thrombo-

cytopenic purpura. In each of these children there has been a gradual spontaneous recovery to a normal blood picture during the first 2 months of life, and following recovery there has been no recurrence of thrombocytopenia up to the present time.

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# American Academy of Pediatrics

## Round Tables

### Round Table Discussion on Infection in the Newborn Period

- Chairman: Stewart H. Clifford, M.D., Boston, Mass.  
Associates: Charles C. Chapple, M.D., Philadelphia, Pa.  
G. D. Cummings, M.D., Lansing, Mich.  
Katharine Dodd, M.D., Cincinnati, Ohio  
Secretaries: Orville E. Barbour, M.D., Peoria, Ill.  
Thomas P. Saltiel, M.D., Chicago, Ill.

CHAIRMAN CLIFFORD.—Infection is a greater hazard to the present generation of newborn infants than to their predecessors. Many factors have conspired to make this so—not only are more babies being born but they are being delivered in hospitals rather than at home and there has been possible no new construction of maternity hospitals to accommodate this increased patient load. There is also a great shortage of both trained nursing personnel and nursery attendants to care adequately for this huge hospital baby population. The resulting crowding and inadequate nursing care have provided conditions most favorable for the occurrence and spread of infection.

In this round table discussion it will be impossible to consider in detail all the types of infection that may affect newborn infants. The infections of the newborn infant that have much in common with those occurring in older infants will be treated in a superficial manner. The main purpose of this discussion is to consider the diagnosis, treatment, and prevention of those infections peculiar to the newborn infant, particularly those causing epidemic diarrhea. To be of value, the recommendations that come out of this discussion cannot be idealistic but must be practical and capable of accomplishment under existing conditions.

The infant may acquire a bacterial, parasitic, or virus infection from any one or more of several sources:

- (1) Infection acquired from the mother either in utero or during the birth process.
- (2) Infection acquired at short range by person-to-person transmission of pathogens through air-borne droplets.
- (3) Infection acquired from pathogens present in the air.
- (4) Infection acquired from physical contact with infected personnel or material.
- (5) Infection acquired from the ingestion of pathogens contained in the food.

#### INFECTIONS ACQUIRED IN UTERO OR DURING THE BIRTH PROCESS

Studies on the mothers of infants with congenital chorioretinitis and other evidence of toxoplasmosis have revealed that six of seven mothers had toxoplasma neutralizing antibodies. This strongly suggests that the mothers were carriers of the parasite and that the parasite was capable of crossing the placental barrier.<sup>1</sup>

Recently, five cases of congenital malaria have been reported from Turkey, in all of which malaria plasmodia were demonstrated in the peripheral blood.<sup>2</sup>

It is well known that the virus of chicken pox and smallpox may pass through the placenta and infect the fetus. The effects of the rubella virus on the embryo have been given wide publicity in recent years. What effect other types of virus infections in the

<sup>1</sup>Heidelman, Joseph M.: Evaluation of Toxoplasma Neutralization Tests in Cases of Chorioretinitis, Arch. Ophth. 34: 28, 1945.

<sup>2</sup>Eckstein, A. and Nixon, W. C. W.: Congenital Malaria, Brit. M. J. 1: 432, 1946.

pregnant woman may have on the fetus is a matter of wide speculation but little factual knowledge.

Syphilis is the most important infection that the fetus may acquire from an infected mother. Dr. Dodd will give special attention to this subject.

In recent years we have observed three mothers with bacteremia or septicemia with infected infants at birth. The organism in one mother was the beta hemolytic streptococcus, her infant had the same organism on blood culture and a streptococcus pneumoniae on post-mortem examination. *Bacillus coli* was the organism in the second mother; her infant had the same organism on blood culture. The third mother's organism was *Bacillus suispestifer*; her infant had a negative blood culture but a positive stool culture for this bacillus. A fourth mother in whom the result of a blood culture was not recorded had an infant with *B. suispestifer* on blood culture shortly after birth. This infant developed a *B. suispestifer* meningitis, from which he died.

There have been two infants who have developed meningococcus meningitis so shortly after birth that one assumes the infection was acquired in utero.

We have encountered a number of instances where the mother has developed an infected amniotic fluid, usually with *Bacillus coli*, and where the infant has been secondarily infected.

The possibility of the infant acquiring an infection during its passage down the birth canal is well known. Gonorrheal ophthalmia is one of the most common infections thus acquired. The infant may also pick up a monilia infection, and Dr. Dodd's recent work presents the disturbing possibility that the virus of epidemic diarrhea may be present in the vaginal mucosa.

#### INFECTIONS ACQUIRED BY PERSON-TO-PERSON TRANSMISSION OF PATHOGENS

The initial bacterial flora of the throat and nasopharynx is largely acquired through direct contact with adults.<sup>2</sup> The newborn infant may acquire an infection from an adult or infant carrying pathogens in his droplets. The most common organism thus transmitted are the *Staphylococcus aureus* and the streptococcus, although others may more rarely be involved. There is considerable evidence that this person-to-person contact is the most important method of spreading virus infection.

#### INFECTIONS ACQUIRED FROM PATHOGENS PRESENT IN THE AIR

The importance of air-borne pathogens in the development of infections in the newborn is difficult to evaluate. Infections of various types can undoubtedly occur by this route but they must be relatively rare.

#### INFECTIONS ACQUIRED FROM PHYSICAL CONTACT WITH INFECTED PERSONNEL OR MATERIAL

The infection of infants by direct contact with infected personnel or material is a very important type of infection. Infections of the skin, mucous membrane, and umbilicus are frequently of this origin. There is a strong suspicion that some varieties of diarrheal disease may be spread by infected nipples and rectal thermometers.

#### INFECTIONS ACQUIRED FROM THE INGESTION OF PATHOGENS CONTAINED IN THE INFANT'S FOOD OR FLUID

In general, the present methods of sterilizing infants' formulae are very unsatisfactory. Recent studies of formula samples showed bacteria counts that would not have satisfied minimum marked requirements for raw milk. A large variety of organisms were recovered from the formulae, in some instances the bacteria were of the same species as those isolated from infants in the nursery as well as from the respiratory tracts or the stools of the personnel. The frequency with which Lancefield Group D streptococci were

<sup>2</sup>Torrey, J. C. and Koser, M. K.: Initial Aerobic Flora of Newborn Infants, Am. J. Dis. Child 67: 82, 1944.

encountered in the throats of infants with epidemic diarrhea suggests infection by the fecal-oral route. Salmonella infection of the newborn is further evidence that poor technique may bridge the gap between the human intestinal tract and the infants.<sup>4</sup>

### Syphilis in the Newborn Infant

Katharine Dodd, M.D.,<sup>\*</sup> Cincinnati

At this point I would like to ask Dr. Dodd to discuss the subject of syphilis in the newborn, following which the rest of the time will be devoted to the problem of diarrhea in the newborn.

The incidence of syphilis in women of child-bearing age has been estimated as about 3 per cent, less than 1 per cent in white women of high economic status and more than 15 per cent in Negro clinic patients.<sup>1</sup> Of the pregnancies occurring in untreated syphilitic women, about 30 per cent will result in death of the fetus and perhaps 80 per cent of those born alive will be infected. If treatment is begun before the fifth month of pregnancy, only about 5 per cent of the offspring will have the disease; if after the fifth month, about 20 per cent. These are the figures given in the prepenicillin days. Early reports of the protection of the child as a result of treatment of the mother with penicillin during her pregnancy were even more encouraging. As more experience accumulates, one is forced to abandon some of the early optimism concerning penicillin as a quick sure-fire cure for syphilis in any stage of the disease. Whether or not the infant will be infected depends not only on the treatment the mother has received but also on the age of her syphilitic infection. Children born of untreated mothers whose syphilis was acquired at the time of conception or during the pregnancy will almost certainly be infected; those born of mothers with congenital syphilis or late latent syphilis will probably escape infection. In the year 1945, 1,870 women were delivered at the Cincinnati General Hospital. Of these, 1,003, or 53.6 per cent, were colored and 867 or 46.4 per cent white. Syphilis was diagnosed because of history or positive serology or both in 178 or 17.7 per cent of the colored women and 59 or 6.8 per cent of the white women. There were thirty more patients in whom the diagnosis of syphilis was doubtful. Twenty-nine of the babies born to the syphilitic women were stillborn. The other 208 became patients in the newborn nursery. The prenatal care given to the mothers varied all the way from excellent to none and the antisymphilitic treatment they had received varied from excellent to none. Many had been treated several years before the present pregnancy but had received no treatment during the pregnancy.

The diagnosis of syphilis in the newborn infant usually presents great difficulties. Clinical signs and symptoms are rarely present at birth. Serology of the mother just before delivery or of cord blood taken at the time of delivery is diagnostic in only about 60 per cent of the infants. They may have syphilis when the serology is negative and may be uninfected even though the serology is positive. Around the years 1933 to 1935 great reliance was placed on roentgenographic changes in the long bones at birth as evidence of syphilis. Ingraham<sup>2</sup> and others were apparently able to pick up by this means many cases of syphilis in infants a few days of age when all other signs were absent or equivocal. My experience both in Nashville and Cincinnati, unfortunately has not duplicated theirs. Only once have I seen a lesion which I thought was undoubtedly the result of syphilis in the roentgenogram of the long bones of a newborn child. That child's mother had been actively treated during the last month of pregnancy. The child's Kahn test, positive at birth, soon became negative and we could only conclude that the infant had probably been infected but had received sufficient therapy during intrauterine life to reverse the

<sup>\*</sup>Rubenstein, A. Daniel, and Foley, George E.: Epidemic Diarrhea of the Newborn in Massachusetts, New Eng. J. Med. 236: 87, 1947.

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<sup>1</sup>Whipple, D. V., and Dunham, E. C.: Congenital Syphilis. I. Incidence, Transmission and Diagnosis, J. PEDIAT. 12: 386, 1938.

<sup>2</sup>Ingraham, N. R., Jr.: Diagnosis of Infantile Congenital Syphilis During the Period of Doubt, Am. J. Syph. & Neurol. 19: 517, 1935.

serology. As we have learned more about the roentgenographic appearance of long bones in conditions other than syphilis, we have become hesitant about the interpretation of minor or even major changes in the long bones. When the child has reached an age of 3 to 6 weeks and the roentgenogram reveals periosteal changes, irregular areas of decreased density at the ends of the long bones and especially an area of decreased density in the proximal, medial aspect of the tibia, syphilis seems to be the only diagnosis tenable. Other clinical signs of disease are by then almost always present. Repeated quantitative Kahn tests and repeated roentgenograms of the long bones combined with careful clinical observation will almost surely rule syphilis in or out by the age of 3 months. It is difficult to follow children this carefully, and even when it is possible one has lost the opportunity to begin therapy early.

The spread of syphilis through contact infection in the nursery rarely presents a problem. The question of treatment of a child who may or may not have syphilis is a problem. If the child has syphilis it is better to treat before signs and symptoms appear and before there is any danger of a fatal outcome because of overwhelming infection. In Cincinnati we try to weigh the infant's chances of infection, using the information we can obtain as to the age of the infection in the mother and the apparent adequacy of the treatment she has received. If the mother has received inadequate treatment, there arises the question whether the child has also received inadequate treatment by the absorption of drugs through the placental circulation. In the days when arsenic and bismuth were the antisyphilitic drugs of choice and one felt that adequate therapy meant at least a year and a half of continuous treatment, we treated only the occasional infant in whom a positive diagnosis could be made at birth. Now, we start penicillin injections if in our judgment there is as much as a 50 per cent chance of the infant's being infected. The child must be kept in the hospital after the mother leaves and has to be weaned from the breast, neither of which procedures we like. We do not know whether we have treated infants who were uninfected. As far as I know we have failed only twice to make a positive diagnosis when syphilis was present. Once the mother and child were discharged before the mother's Wassermann and Kahn tests had been reported and once the mother's Kahn test was reported as negative although she was infected. Before we adopted our present plan, three syphilitic infants had returned to the hospital with severe infection. One died in spite of therapy. The ideal way to deal with the problem of syphilitic infection in the newborn nursery is to prevent its occurrence by adequate care of the pregnant woman. That is a task for the obstetrician, the adult syphilologist, and the public health authorities. They should receive every encouragement from us. Meanwhile, the diagnosis and therefore the management of syphilitic infection continues to be a difficult problem in the newborn infant.

#### DISCUSSION

DR. J. C. JAUDON, ST. LOUIS.—When a diagnosis of syphilis is made, how is the infant treated?

DR. DODD.—At present we do not wait to make a definite diagnosis of syphilis but treat the child if we think he probably has syphilis. We are using intramuscular doses of penicillin given every three hours. The dose is 10,000 units every three hours for pre-matures and 15,000 units for full-term infants. We give a total of at least 1.6 million units to pre-matures and 2.4 million for full-term infants. It usually takes between fourteen and twenty-one days to complete the therapy.

DR. H. KENNEDY, JR., BIRMINGHAM, ALA.—Do you follow up the treatment with bismuth, arsenic, etc.?

DR. DODD.—We have not done so as yet but are just beginning to give bismuth and arsenic along with the penicillin.

DR. CLIFFORD.—What do you do if Wassermann or Kahn is positive after penicillin?

DR. DODD.—The Wassermann of the children who have negative tests before treatment has not become positive at completion of treatment. We follow these children with quantitative Kahn tests and use the criterion of a rise in titer or recurrent positive after we have negatives as evidence of relapse. None of our children have relapsed since we have used the larger dosage but most have not as yet been followed for a very long time. Most of the titers have ultimately become negative.

DR. CLIFFORD.—Is there a law in Ohio requiring a Kahn test on all pregnant women?

DR. DODD.—There has been one since November, 1945, but the law is not obeyed well and a good many of the women do not go to a doctor for prenatal care.

DR. R. A. HIGGONS, PORT CHESTER, N. Y.—In what length of time is the dosage given? How divided? How long do you stand pat on the treatment?

DR. DODD.—The first two parts of this question have already been answered. We have treated a few children a second time when the Kahn tests have been positive after nine months.

DR. CLIFFORD.—How valuable do you find the quantitative tests?

DR. DODD.—Quantitative tests done immediately after birth have not proved very valuable. We have had some babies with negative serology who have later developed syphilis. Unfortunately, most of the children have not been brought back until symptoms of syphilis developed, at which time the Kahn test has been strongly positive. Quantitative serology has apparently proved of value in following results of treatment. The children who have shown a steadily falling titer have so far stayed well. We really do not have enough cases to permit a very authoritative answer to this question.

DR. CLIFFORD.—The State should assume the responsibility of the follow-up observation of syphilitic infants. How would you regulate the treatment, Dr. Cummings?

DR. CUMMINGS.—Unless syphilitic infants can be followed by their own physicians, it would seem necessary to recommend that the follow-up become responsibility of the local health officer and his staff. Presuming that the initial treatment of the case was adequate, I would follow syphilitic infants clinically and by means of quantitative blood testing at periodic intervals. I believe it is the custom in the rapid treatment of adults to do a quantitative blood test once a month for six months, then once at the ninth month, once at the twelfth month, once at the eighteenth month and finally at the end of two years.

#### Epidemic Diarrhea of the Newborn Infant From the Point of View of the Clinical Investigator

Katharine Dodd, M.D.

By far the most serious infection which occurs in the newborn period is diarrhea. While the death rate for diarrhea in infants up to one year of age has been falling for the last 15 years and the death rate for infants under one month from all causes has also fallen, although at a slower rate, the diarrheal death rate for infants under one month has risen gradually during the same period. Epidemics of diarrhea occur in newborn nurseries in all countries. As visitors have come to us at the Cincinnati Children's Hospital since the end of the war, one of the most frequent questions has been, "What do you think is the cause of diarrhea of the newborn and what can be done to prevent it or treat it when it occurs?" Two visitors from foreign countries cited appalling figures of death rates from diarrhea of more than 30 per cent of the babies born in two large cities during a war year. In New York City, 9,236 newborn babies were reported to have been exposed to the disease by 1941.<sup>1</sup> Of these, 1,233 contracted the disease, a morbidity

<sup>1</sup>Frant, S., and Abramson, H.: Epidemic Diarrhea of the Newborn, in Brennemann's Practice of Pediatrics, Hagerstown, Maryland, 1945, W. F. Prior Company, Inc., v. 1, chap. 28, p. 19.

rate of 13.4 per cent, 540 of the babies died, a case fatality rate of 43.6 per cent, and a mortality rate of 5.8 per cent for the babies exposed. As one glances through medical journals one frequently comes upon a reference to an epidemic in one city or another. One of the last I noted was in the October issue of the *Journal of the American Medical Association*<sup>2</sup> where the following report from California appears under "Medical News." "On September 25 the Oakland Health Department closed and quarantined the maternity ward and nursery of the *Providence Hospital* in an effort to halt a mysterious outbreak of disease which has already killed six of seventeen babies afflicted with it since September 15. The disease has not been completely classified but its main symptom is diarrhea." In the first two years I was in Cincinnati there were three epidemics of diarrhea of the newborn as a result of which infants were admitted to the Children's Hospital. In one epidemic fourteen children came to our infant ward from one newborn nursery; all within a period of three days. A similar number were admitted to an improvised isolation ward in the hospital concerned. One-third of the children whom we cared for died. During the same two years three mild epidemics occurred in the newborn nursery of the Cincinnati General Hospital. None of the full-term infants was very ill but eight premature infants born in the same delivery room but cared for in a separate nursery by different personnel all contracted the disease and four of the eight died.

It is questionable whether epidemic diarrhea of the newborn constitutes a single entity. Bacteria present in milk, on the hands of nurses and doctors, or passed from mother to child during the process of birth or later may cause illness in which diarrhea is the chief symptom. In a recent epidemic<sup>3</sup> in Great Bend, Kan., involving twenty-four infants, nine of whom died, milk for 90 per cent of the community came from two dairies. On investigation it was found that the milk was inadequately pasteurized, contaminated after pasteurization, and sold in unsterilized bottles. Diarrhea was rampant throughout the town. Prior to every outbreak in the nursery, except one, a mother or nurse on the obstetric floor developed diarrhea. *Pseudomonas aeruginosa*, the organism which most of us know as *Bacillus pyocyaneus*, was apparently the causative agent of the diarrhea. It was isolated from two-thirds of the babies' stools and from the liver, spleen, and gall bladder of two infants on post-mortem examination. Various other organisms such as *Salmonella* and *Proteus* were found in some of the stools. It was thought that the babies acquired the infection from adults who cared for them rather than directly from the milk. This seems a shocking instance of what may happen when public health authorities become lax in these days when the public must rely on them for protection against contamination of both milk and water. It also sounds as if the technique employed in the hospital nursery must have been very poor. Cases of diarrhea in which pathogenic organisms have been isolated from the stools and at times from the blood stream have been reported from several other nurseries. Various types of dysentery bacilli and *Salmonella*, *Bacillus lactis aerogenes*, *Bacillus dispar*, and *Proteus morgani* have been some of the offenders. Interestingly enough, rarely did a real epidemic of diarrhea arise. Either the diarrhea concerned one baby when his mother also had diarrhea at the time of delivery or had organisms in her stools similar to those isolated from the baby. Sometimes one or more babies in adjoining cribs also became ill. However, according to one report<sup>4</sup> an entire nursery population of six babies contracted diarrhea due to a *Salmonella* organism. A nurse who was not ill but had the organisms in tremendous numbers in her stools was the probable source of infection. Four of the infants recovered and two died. In another epidemic<sup>5</sup> which concerned thirty-four infants, fourteen of whom died, *Bacillus mucosus*

<sup>2</sup>"Medical News," J. A. M. A. 132: 399, 1946.

<sup>3</sup>Ensign, P. R., and Hunter, C. A.: An Epidemic of Diarrhea in the Newborn Nursery Caused by a Milkborne Epidemic in the Community, J. PEDIAT. 29: 626, 1946.

<sup>4</sup>Abramson, H., Frant, S., and Oldenbusch, C.: *Salmonella* Infection of the Newborn: Its Differentiation from Epidemic Diarrhea and Other Primary Enteric Disorders of Newborn, M. Clin. North Am. 23: 591, 1929.

<sup>5</sup>Jampolis, M., Howell, K. M., Calvin, J. K., and Leventhal, M. L.: *Bacillus Mucosus* Infection of the Newborn, Am. J. Dis. Child. 43: 70, 1922.



was thought to be the causative agent. The organism was cultured from the stools and from the throats of three nursemaids. No further cases occurred after their removal from the nursery. *B. dyspar* was recovered from the stools of thirty six infants in an epidemic reported by Schwenker<sup>6</sup> in Baltimore. Unfortunately, no details of the epidemic are given except for the fact that twenty one of the infants died.

A recent survey of epidemic diarrhea of the newborn in Massachusetts<sup>7</sup> revealed many inadequacies in nursing care in nineteen epidemics studied. Overcrowding, insufficient personnel, general use of a common thermometer, and inadequate supervision of formula making were frequently encountered. Laboratory examinations of sterilizing solutions, including alcohol hand solution and thermometer dips, formulas, and nipples showed heavy bacterial contamination. Nevertheless, no particular pathogenic organism was consistently isolated from the babies' stools in any of the epidemics. Similarly, no pathogenic bacteria have been demonstrated by most careful bacteriological technique in most instances where the outbreak of diarrhea has been widespread. The infant's stools, nasopharynxes and blood, the nasopharynxes and stools of all attendants, the bottles, nipples, and milk used in formula feedings, have often all been cultured but only the usual bacterial flora found. At times it has been suggested that organisms, such as colon bacilli, which are nonpathogenic for adults might be pathogenic for infants who have as yet acquired no immunity to them. If this were true it would be difficult to explain why a large number of babies in a nursery should suddenly develop diarrhea whereas at another time no diarrhea occurs in spite of the fact that the same type of organisms are present in the babies' stools at both times. Epidemic diarrhea must be caused by an infectious agent present at some times, absent at others and capable of spread from infant to infant by one means or another.

The symptomatology of diarrhea of the newborn has usually varied little from one epidemic to another. Breast and bottle fed babies are attacked equally. The incubation period usually appears to be short, a matter of four days or less. Occasionally an infant has diarrhea almost from birth. At the outset of an epidemic the infants usually begin to have loose stools on the third day—the time when loose stools transitional from meconium to fecal stools may well be a normal finding. For this reason the abnormal stools are often ignored until the infants begin to look ill or diarrhea develops in older infants who had previously been doing well. Sometimes, particularly now when many obstetrical patients are discharged from the hospital on the fourth or fifth day after delivery, the first intimation that there is an epidemic of diarrhea comes when several babies recently discharged from a nursery develop diarrhea at home. The diarrheal stools number from three or four to nine or ten a day. They are usually green and watery and are expelled with explosive violence. Some authors have emphasized the absence of mucus and blood, but it has been my experience and that of some others that the stools often contain large amounts of mucus and may at times be streaked or flecked with blood. Occasionally the stools are not loose but are heavily blood streaked. In a severe epidemic dehydration, acidosis and listlessness follow closely upon the heels of the diarrhea. The infants refuse to nurse and may vomit. As the disease progresses otitis media, pneumonia, or even septicemia caused by secondary invaders may develop. Post mortem examination of fatal cases reveals slight pathological changes. There are often congestion and swelling of the small bowel, especially of the jejunum and ileum. Occasionally small, shallow ulcers are seen. On microscopic examination there is congestion of the mucosa and submucosal bed with edema of the submucosa. Widely scattered small foci of necrotic cells may be noted as well as small areas of hemorrhage just beneath or upon the mucosal surface. There is usually a slight polymorphonuclear leukocytic infiltration of the submucosa. No intracellular inclusions have been noted. In infants dying late in the disease bronchopneumonia is often found.

<sup>6</sup>Schwenker, I. T. Dysentery Due to *Bacillus Dyspar*. *Am J Dis Child* 70: 1321, 1935.

<sup>7</sup>Rubenstein, A. D. and Foley, G. E. Epidemic Diarrhea of the Newborn in Massachusetts. *New England J Med* 236: 87, 1947.

A virus etiology for most epidemics of the disease has been suspected for the last ten years. Lyon and Folom<sup>1</sup> described three epidemics which occurred at a time when clinical influenza was unusually prevalent in the community and suggested that the malady was an expression of infection with the influenza virus in the newborn. Light and Hodes<sup>2</sup> in 1943 reported the first apparently successful isolation of a filterable virus from stools collected from infants in four separate epidemics of varying severity. Calves were injected intranasally with Sertz filtrates of the stools. A bloody mucoid diarrhea ensued in two to five days. The constitutional reaction was, as a rule, minimal. The disease was relapsing in nature and lasted from eight to fifty four days. Successive calf passage was readily accomplished with both filtered and unfiltered material. Following recovery, large doses of active material failed to cause disease. Cross immunity studies indicated that the four strains were apparently identical. Sera obtained from six babies following convalescence conferred complete or partial protection from intranasal infection of the animals. It was thought that a somewhat similar diarrheal disease indigenous to calves and caused by a virus was ruled out as the etiological agent of the disease in the calves studied.

Buddingh and Dodd<sup>3</sup> were able to produce lesions on the scarified cornea of rabbits with an inoculum of stool obtained during an epidemic of diarrhea in one of the nurseries for newborn infants at Vanderbilt. The agent was readily filterable through Berkfeld V candles. Similar lesions of the cornea had been produced earlier with swabbings from the mouth and stools of older infants with a mild stomatitis and diarrhea. Within twenty four hours of inoculation haziness with cloudy opacity developed along the lines of scarification of the cornea, hyperemia and swelling of the conjunctiva, and in many instances an intense iritis developed. The reaction persisted for about forty eight hours. Microscopic sections showed nonspecific congestion, edema, and infiltration with polymorphonuclear cells. Strains of the agent were maintained for as many as forty five serial passages. Immunity developed in the rabbit eye in a period of three weeks. Serum obtained from twelve patients during the acute disease failed to prevent a reaction in the rabbit cornea when mixed with virus; similar mixtures using serum obtained during convalescence produced no lesion. Attempts to propagate the virus in other animals or in the developing chick embryo have so far been unsuccessful. The filterable agent has been isolated by Buddingh from stools obtained from epidemics in Nashville, Memphis, Cincinnati, and Boston. Cross immunity has been demonstrated between all strains regardless of whether the death rate in an epidemic was none or over 50 per cent. It has not been possible to test whether the two viruses isolated by Light and by Buddingh are the same. It seems probable that a virus is the usual etiologic agent in epidemic diarrhea of the newborn but it may be that, as in encephalitis, different viruses are concerned in different epidemics.

Until the etiologic agent of diarrhea of the newborn can be readily demonstrated, the mode of spread will remain difficult to establish. The usual method of dealing with an epidemic is to quarantine the nursery and often the maternity ward as well. In the meantime the babies are cared for in the quarantined nursery, transferred to the infants' or children's wards in the same hospital, or admitted to other hospitals in the city. I should like to interject a word of caution concerning the last two procedures. Frant states in an article in Brennemann's Pediatrics that no adult in contact with babies suffering from diarrhea of the newborn has contracted the disease nor have there been any cases among older infants and children in the open pediatric wards in which these children were cared for. This has not been our experience either at Vanderbilt or in Cincinnati. In the first nursery epidemic studied by Buddingh and Dodd, mouth swabs from three of the four nurses in charge of the nursery were found to produce a typical reaction in rabbit eyes. One of the

<sup>1</sup>Lyon, G. M., and Folom, T. G. Epidemic Diarrhea of the Newborn. Clinico-epidemic, Pathologic and Therapeutic Aspects, *Am. J. Dis. Child.* 61: 427, 1941.

<sup>2</sup>Light, J. S., and Hodes, H. L. Studies on Epidemic Diarrhea of the Newborn. Isolation of the Filterable Agent Causing Diarrhea in Calves, *Am. J. Pub. Health* 33: 1451, 1943.

<sup>3</sup>Buddingh, G. J., and Dodd, K. Stomatitis and Diarrhea of Infants Caused by Hitherto Unrecognized Virus, *J. Pediatr.* 25: 105, 1944.

<sup>4</sup>Buddingh, G. J. Virus Stomatitis and Virus Diarrhea of Young Children, *South M. J.* 39: 382, 1946.

nurses apparently carried the infection home to her 6- and 8-year-old daughters. Four other adults who were subsequently in close contact with infected infants developed a mild stomatitis which was proved to be positive for the virus. In every instance infants of varying ages cared for by these four individuals became ill with diarrhea. When newborn infants with diarrhea have been admitted to the infant ward either at Vanderbilt or Cincinnati, secondary cases of infection have always developed on the ward in infants varying in age from a few days up to at least 6 months. Premature infants cared for in a separate, well-isolated nursery but attended by the same doctors and nurses as the sick infants, have developed diarrhea even though they were often a month or two old at the time of exposure. The disease has been severe in the premature infants and the fatality rate is usually high.

Because the first cases in a nursery have often developed in babies of 2 to 3 days of age, we thought that the babies might be acquiring their infection during passage through the birth canal. In thrush and inclusion blennorrhea, infection is known to occur in this manner. In many of the reported instances of diarrhea of the newborn infant caused by pathogenic bacteria, infection was almost certainly acquired during the birth process. With the possibility in mind that the mother might harbor the virus infection in her vagina, swabbings were obtained from the mouth and stools of the infant and from the vagina of the mother when diarrhea developed in the newborn nursery in Cincinnati. The swabs were sent to Dr. Buddingh by air mail. Virus was isolated on rabbit corneas from the material obtained from both mother and child and identified by cross protection tests. If the birth canal of the mother should prove to be a common source of infection for the infant, the prevention of diarrhea in nurseries will indeed present a difficult problem. Small nursery units, extreme care in hand washing and precautions against contamination with mouth secretions may prevent wide dissemination of infection but single cases will continue to occur unless by some miracle an antibiological can be found which will prevent virus infections. Immune globulin may prove of some value in the prevention of infection. The initial trial by High, Anderson, and Nelson<sup>11</sup> did not lead to beneficial results.

My experience in many different newborn nurseries is not wide. I have never seen a serious epidemic develop in a nursery where the babies were carefully watched by pediatricians even though the physical facilities except for the presence of plenty of soap and water for hand washing were poor. The serious epidemics I have seen have arisen in nurseries where the babies were cared for by doctors whose interest was primarily in the mother rather than the infants. In the most serious epidemic I saw the story as given by the parents was, "We thought the baby was doing well, but on the way home he had four or five loose, watery stools and has continued to have diarrhea ever since." Surely some of the diarrhea must have developed before the babies left the hospital but was unnoticed in the busy, overcrowded nursery. Three epidemics reported from the New York Hospitals<sup>12</sup> where the infants are carefully watched by pediatricians, carried a very low death rate—none except among premature infants. Perhaps I have just been fortunate, and next week or next month severe diarrhea will strike in the nursery at the Cincinnati General Hospital where the babies are seen daily by the pediatricians and in spite of overcrowding and poor physical facilities hand washing is rigorously carried out. I should like to believe that disastrous epidemics will not occur while we adhere to our present watchfulness and techniques.

The treatment of diarrhea requires, I am sure, as well or better trained personnel than does its prevention. Some infants continue to nurse and gain well in spite of the passage of an increased number of somewhat watery stools containing large amounts of mucus. Such infants should be carefully watched but their food and fluid intake left undisturbed. Others, the premature infants in particular, rapidly develop the same dehydration, acidosis, apathy or restlessness that occurs in all severe diarrheas of infancy. They must receive a course of carefully planned and carefully executed therapy. Opinions differ as to how long infants

<sup>11</sup>High, R. H., Anderson, N. A., and Nelson, W. E.: Further Observations of Epidemic Diarrhea of the Newborn. I. Observation of a Biphasic Type of Clinical Course. II. Therapeutic Measures Including Prophylactic and Therapeutic use of Gamma Globulin, *J. PEDIAT.* 28: 467, 1946.

<sup>12</sup>Baker, C. J.: Epidemic Diarrhea of the Newborn, *J. PEDIAT.* 14: 183, 1939.

with diarrhea should be starved, what amounts of normal saline, glucose solution, and whole blood and plasma, or at times solutions of casein hydrolysate should be administered and in what order they should be given. Perhaps by now the role of potassium-containing solutions in the treatment of diarrhea is more thoroughly evaluated than it was last year and they too should be used in therapy. In spite of occasional favorable reports of the influence on mortality figures of various chalk and apple mixtures it is difficult for me to believe from my experience or knowledge of diarrhea in the newborn that these remedies can exert any favorable influence on the primary infection. In spite of some favorable reports on the use of various sulfonamides, I doubt if they exert any influence on the course of the diarrhea except in the rare instances where diarrhea is caused by bacteria which are sensitive to sulfonamides.

Our plan of therapy in Cincinnati is to stop all oral intake in the dehydrated infants and treat by means of parenteral fluid intake. Information on electrolytes and total osmotic equilibrium is obtained by means of carbon dioxide, chloride, and nonprotein nitrogen determinations. Initially, in order to avoid embarrassment of the circulation of severely dehydrated patients by the use of hypertonic solutions, 50 to 100 c.c. of physiological saline are administered rapidly. The acidosis is then corrected by not more than twenty volumes per cent by the administration of 3.7 per cent sodium bicarbonate solution. In patients with moderate acidosis sodium lactate is often used. In the first twenty-four hours saline containing fluids in amounts equal to 5 to 10 per cent of the body weight in addition to the basal requirement of 100 to 150 c.c. is given. The total fluid requirement for twenty-four hours of 150 c.c. per kilogram of body weight is made up by the use of 5 per cent glucose in 100 to 300 c.c. amounts administered alternately with the saline in order to spread the electrolyte administration evenly throughout the day. In most cases, blood, plasma, casein hydrolysates, and hypertonic solutions of glucose or glucose in saline are used only when dehydration is largely overcome. In cases of severe circulatory collapse or anemia blood and plasma are occasionally given in the first twenty-four hours. The intravenous infusion is continued until the infant is well hydrated and the diarrheal stools have ceased or at least greatly lessened in frequency and water content. While the diarrhea continues, one and a half of two times the basal amount of electrolyte is supplied as normal salt solution or the saline contained in blood or plasma. The infants are carefully watched for the appearance of edema, the recurrence of diarrhea, and the development of any untoward symptoms. Chemical checks of the chloride, carbon dioxide, nonprotein nitrogen and protein content of the plasma are made as indications arise. Because we have found that hypocalcemia with symptoms of tetany often develops during the postacidotic phase, the serum calcium is also determined if the baby becomes irritable, unduly drowsy, or has symptoms of collapse or convulsions. A dilute solution of calcium chloride is given by gavage, or in desperate cases dilute calcium gluconate or calcium chloride by vein when such symptoms occur. We think the administration of calcium has been lifesaving in many instances.

No exact rules are followed as to resumption of feedings. We prefer when possible to delay oral intake until the diarrhea has ceased and to start the feedings while the intravenous infusion is still in place. We usually begin with 15 to 30 c.c. of water or glucose in water to avoid aspiration pneumonia in case the baby vomits. If this is well taken, equal amounts of an easily digested formula such as skimmed or half skimmed milk and sugar is offered. The amount is gradually increased, the baby's fluid and electrolyte requirement being made up by the continuing intravenous infusion or by the use of subcutaneous fluids. Sulfadiazine is usually administered for the first few days until it is established by culture that there are no dysentery organisms in the stools. Penicillin injections are given at the least suspicion of secondary infection but are not used routinely. As diarrhea of the newborn has a tendency to relapse one sometimes has to stop all feedings and start treatment again from the beginning. We have fortunately not had the opportunity to treat a large number of babies from a severe epidemic since the adoption of all the details of our plan but feel fairly confident that if fourteen more babies should arrive on our ward as sick as these we saw nearly two years ago we could now save more than two-thirds of them.

## Epidemic Diarrhea of the Newborn from the Point of View of the Epidemiologist and Bacteriologist

G. D. Cummings,\* M.D., Lansing, Mich.

The material to be presented here was gathered by the Diarrhea and Enteritis Study Group of the Michigan Department of Health Laboratories. This study group was organized four years ago for the specific purpose of attempting to determine the etiology of the clinical entity known as epidemic diarrhea of the newborn. The group was financed jointly by the Kellogg Foundation and the Michigan Department of Health Laboratories.

Study personnel were organized into two integrated units. One unit was composed of physicians, nurses, and clerks for the purpose of studying hospital outbreaks. The other unit was composed of laboratory personnel for the purpose of analyzing the various specimens collected by the medical group.

During the first year of the program it became evident that the group would be called upon to study a wide variety of outbreaks, some involving newborn nursery patients; others involving pediatric patients.

It soon became evident also that the study of infants suffering from the various types of gastroenteritis should be paralleled by a study of a normal newborn population. Accordingly, arrangements were made with a local general hospital whereby the study group could collect certain data on normal newborn infants. This latter study was responsible for the ultimate interest of the study group in nursery techniques, and for the position the group now takes on the subject of infection control in nurseries.

This discussion will be limited largely to studies on the etiology of the various types of infant gastroenteritis and to studies on methods for preventing or controlling nursery infection.

### STUDIES ON ETIOLOGY

The epidemics studied by our group can be classified into three categories:

- a. Epidemics caused by various members of the *Salmonella* group.
- b. Epidemics of true epidemic diarrhea of the newborn.
- c. Epidemics with no clear-cut etiology.

*Salmonella* Outbreaks.—The wide interest in the etiology of epidemic diarrhea of the newborn has, in a way, served to obscure the importance of the *Salmonella* group in infant gastroenteritis. This has been particularly true in the smaller hospitals where adequate laboratory facilities were not available. We have observed one nursery outbreak caused by *Salmonella panama* and a number of pediatric outbreaks caused by various members of the *Salmonella* group.

The *S. panama* outbreak was observed in a nursery in a Michigan hospital in March, 1944. The first cases observed were cases of meningitis and not of diarrhea. The assistance of the Department of Health was requested on the basis of the meningitis. A careful study of the situation revealed both meningitis and diarrhea occurring in the same infants. It also became obvious that diarrhea, meningitis or both had been observed sporadically for the previous six months. Local reports were that diarrhea had been rampant six months prior to the investigation. Autopsy material from three deaths, which occurred in March, yielded *S. panama* in blood, spinal fluid, meninges, lung tissue, and feces. *S. panama* was also recovered from the stools of our graduate nurse, one nurses' aide and one maid. In addition, the organism was recovered from eight well newborn infants and two well mothers of these infants. Altogether, twelve infant deaths could be attributed to this organism. *S. panama* was isolated from the stools of two other infants hospitalized in two other cities. Investigation revealed that these infants were born in the hospital under investigation. The outbreak was brought to a close by the removal of the carriers among the personnel. It is interesting to note that every strain of *S. panama* which we have isolated since this outbreak in 1944 has come from an individual having his origin in the city in which the nursery outbreak occurred.

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More recently we have had an opportunity to observe two cases of *Salmonella typhimurium* in infants in a pediatric section of a general hospital. One of these infants was admitted as a boarder and the other with a possible case of pyloric stenosis. The first infant had two distinct episodes of diarrhea with elevated temperatures, the first occurring about five weeks after admission. Following the second episode, a stool examination revealed *S. typhimurium*. The organism has remained present in the stools to the present time, or a period of approximately ten weeks. The second patient was placed in the same room with this patient about the time the laboratory began to report not *S. typhimurium* but *Salmonella typhimurium* var. *copenhagen*. Two weeks after admission, the second patient had a mild episode of diarrhea and the laboratory reported *S. typhimurium* var. *copenhagen* as present in the stools. The second patient was clearly a victim of cross-infection, since his admission stool had been negative. The stools of these infants still contain, *S. typhimurium* var. *copenhagen* at the present time, although both infants are clinically free from diarrhea. A stool survey of pediatric nurses revealed one nurse whose stool contained *S. typhimurium* and who reported a previous episode of diarrhea.

This type of small outbreak has been observed rather commonly and emphasizes the necessity for carrier control among hospital personnel.

*Epidemic Diarrhea of the Newborn.*—A number of outbreaks of true epidemic diarrhea of the newborn have been observed and two are worthy of mention.

The first outbreak occurred in the premature section of a children's hospital. This outbreak occurred at a time when it was impossible to obtain newborn calves for experimental use after the method of Light and Hodes.<sup>1</sup> As a result, material obtained from infants was tested only in the smaller laboratory animals. The rabbit corneal test was also included, based upon the work of Buddingh and Dodd<sup>2</sup> in the realm of stomatitis and diarrhea, although none of the infants exhibited a clear-cut stomatitis. All of the animals tested were negative but the corneal test revealed some interesting findings. Seitz filtrates of pools of infant stools gave positive eye reactions as described by Buddingh and Dodd. Subsequent experience with serial passages of corneal material, however, led us to believe that the test was erratic if not nonspecific. As a result, a large number of rabbit corneas were tested with trauma, trauma and alundum, stools from normal infants, normal infant mouth washings, strains of *Monilia*, coagulase positive staphylococci, hemolytic streptococci and coliform organisms. It was possible with all of these specimens or techniques to produce what we considered to be typical positive reactions as described by Buddingh and Dodd. We were unable also to obtain consistently positive eye reactions on serial passage with stool material from infected infants or from control material. Our conclusion at the end of a series of experiments which involved 1,500 rabbits was that the rabbit corneal test was nonspecific unless it could be confirmed by the presence of intracytoplasmic or intranuclear inclusion bodies.

We were, therefore, unable to isolate a specific etiologic agent in this outbreak.

One interesting clinical observation was made. The study group assisted the hospital in establishing new techniques in the reopened nursery. The chief nurse of the study group acted as supervisor of the premature nursery for a period of twelve weeks. This period of time was selected because there had been three consecutive outbreaks all of which appeared approximately six weeks following each reopening. Over the period of twelve weeks there were no new cases of epidemic diarrhea of the newborn. However, on two adjacent wings on the same floor there developed nine and nine cases, respectively. These cases, however, developed in infants older than one month of age. There were no positive laboratory findings and the clinical picture was that of epidemic diarrhea of the newborn. Because the generally accepted definition of epidemic diarrhea of the newborn limits the disease to neonatal infants, these cases were classified as house or endogenous diarrheas.

The second outbreak occurred in the smaller of two nurseries in a general hospital and involved twenty-two babies. Test material was obtained during the first twenty-four hours

<sup>1</sup>Light, Jacob S., and Hodes, Horace L.: Studies on Epidemic Diarrhea of the Newborn: Isolation of a Filtrable Agent Causing Diarrhea in Calves, *Am. J. Pub. Health* 33: 1451, 1943.

<sup>2</sup>Buddingh, G. J., and Dodd, K.: Stomatitis and Diarrhea of Infants Caused by a Hitherto Unrecognized Virus, *J. PEDIAT.* 25: 105, 1944.

and before therapy was begun. Nose, throat, and stool specimens obtained were free from bacterial pathogens. Pooled material was tested for viruses in mice, monkeys, guinea pigs, baby chickens, cotton rats, chick embryos, hamsters, newborn pigs, and newborn calves. This one experiment involved approximately 1,500 animals. All of the animals or media reacted negatively except the calves. The first passage included four test calves and four control calves. The four test animals came down with diarrhea in one to three days and were acutely ill. Stools were watery yellow in character and occasionally contained flecks of blood. All of the control animals remained well. Stool material from the four infected animals was subsequently passed through five serial passages in calves with the production of diarrhea. The sixth and subsequent passages, however, failed to produce diarrhea and the agent involved either lost potency or was lost in passage. Inocula included unfiltered stool suspensions, Seitz filtered suspensions, and ultracentrifuged bacteria-free suspensions. The agent causing the calf diarrhea, therefore, appeared to be filtrable. We were satisfied in this single experience that we were dealing with a filtrable agent of the type described by Light and Hoëes although we were unable to maintain the potency of this agent.

It is interesting to note that of the twenty-two babies involved in this outbreak, four also had impetigo, two conjunctivitis and one had an upper respiratory infection.

*Epidemics with no Clear-cut Etiology.*—A number of outbreaks of neonatal diarrhea were observed which could not be called clinical epidemic diarrhea of the newborn and which were not caused by any well-defined pathogen. These outbreaks were usually mild in type, explosive in onset, short in duration, and without fatalities. Daily stool totals were usually not markedly increased and stools were semiliquid-green in character rather than liquid yellow. Nose, throat, and stool specimens were negative for the accepted bacterial pathogens. It was customary, however, to isolate a variety of organisms from these specimens which aroused considerable speculation as to their etiologic significance. This group included coagulase positive staphylococci, hemolytic streptococci, various strains of *Proteus*, *Salmonella alkalescens*, *Bacterium alkaligenes* and various coliform organisms. These organisms were also routinely recovered from the various supplies, equipment, and solutions of the nursery. In one nursery, for example, *B. alkaligenes* was isolated from twenty-four infant stool specimens, fifteen meconium specimens, one infant nose specimen, three nurse stool specimens, and three nurses' aide stool specimens. It was also isolated from nursery basins, enema solutions, subcutaneous saline solutions, soap solution, table tops, and hand brushes.

It has gradually become the opinion of the study group that this type of outbreak is due to massive bacterial contamination with organisms usually considered to be of low or absent pathogenicity, together with a complete absence of the usual nursery techniques. It is felt that filth in the nursery is the principal contributing factor.

#### STUDIES ON METHODS FOR PREVENTING NURSERY INFECTION

As a preliminary to the study of these infants, it was necessary to standardize nursing techniques, especially those relating to infection control. The term technique was defined broadly in order to cover all of the potential routes of infection to the nursery population. An attempt was made to visualize all of the possible infection routes and then to establish the proper barriers to these routes outside the physical units containing the infant population. As a result, emphasis was placed on the following points:

1. *Expert Nursing Supervision.* Four specially trained graduate nurses were placed in charge of the nursery, one acting as general supervisor. It was felt that the entire success of the project would depend on these nurses and subsequent experience confirmed this opinion.

2. *Adequate Nursing Personnel.* Student nurses were assigned to the nursery in a ratio of one nurse for every eight mature infants and one nurse for every four premature infants. This ratio has been rigidly maintained over the four-year period.

3. *Infection Control Among Nursery Personnel and Mothers.* Each shift supervisor was assigned the responsibility for determining the presence of infection among nurses and mothers. Nurses were questioned directly regarding upper respiratory infection or diarrhea. No nurse was permitted to go on duty following a report of any type of infection. The gen-

eral supervisor questioned the mothers daily for the presence of infection. When infection was evident, babies were placed on bottle feeding only or placed in isolation if continued at the breast. In short, a definite effort was made to prevent individuals with frank infection from actually contacting the infant population.

4. *Carrier Control Among Nurses and Mothers.* Nose, throat and stool specimens were collected from nursery personnel monthly and from mothers at admission. It was felt that this was a particularly important procedure in view of the rather high incidence of *Salmonella* infections in adults.

5. *Formula Sterilization.* It was decided to steam sterilize all formulas, except those containing lactic acid. Formulas were sterilized as integrated units, that is, the bottle containing the formula was nipples and covered at the time of sterilization. Formulas were then autoclaved at 121° C. for eight minutes. This sterilization period was determined by laboratory tests for sterility.

6. *Daily Rounds on Infants.* The general supervisor was assigned the responsibility of observing each infant at bathing time for abnormal signs and for charting suspicious signs accurately. It was felt that the supervisor, by this method, would have the best opinion on the condition of each infant.

7. *Isolation of Infected Infants.* Infants with obvious signs of infection were immediately isolated. Infants with four or more abnormal stools in twenty-four hours were also isolated. Skin lesions were inspected carefully and infants with as few as one or two true pustules were also placed in isolation.

8. *Hand Technique.* Hand technique in the nursery was rigidly enforced. Each nurse was expected to wash her hands carefully with soap and running water after each baby and between each baby and contaminated objects. Each nurse and all other individuals entering the nursery were required to scrub hands and arms for five minutes with a brush, soap, and running water, and to wear sterile caps, masks, and gowns.

9. *Charting.* The general supervisor was required to insist on accurate charting. It was appreciated that accurate charting is of real value in determining the presence of an epidemic.

10. *Cleanliness.* Absolute cleanliness was insisted upon and it was required that the nursery be kept clean by wet mopping and dusting. Contact points where infants might become infected were cleaned with germicidal solutions.

11. *Sterile Supplies.* All linens and other supplies not affected by steam were sterilized for one hour at 121° C.

12. *Visitor Control.* Visitors were limited to two grandmothers and the father. By this method, the variety of outside adult contacts to the mother and baby was markedly reduced.

Once this general plan was in operation, an attempt was then made to evaluate the influence of this plan, if any, on the incidence of infection in the infant population. Each infant was observed daily for evidences of infection. A nose, throat, and stool specimen was taken routinely on each infant on the first day of life and every three days thereafter during his nursery stay. All suspicious skin lesions and eye drainages were cultured. The ultimate objective was to attempt a correlation between technique on the one hand and clinical and laboratory findings on the other. After fifteen months of experience a correlation was attempted between the incidence of all types of clinical infection and positive laboratory findings on fourth-day infant stools. The fourth day stool was selected to avoid culturing meconium specimens and to cover the greatest possible total of babies. Stools were called positive when they contained coagulase positive staphylococci, beta hemolytic streptococci and the accepted enteric pathogens of the *Salmonella* and *Shigella* groups. The only pathogenic organism recovered in the fifteen-month period was the coagulase positive staphylococcus and there appeared to be a close correlation between the presence of this organism and the amount of clinical infection. Thus, at the beginning of the period there were forty-three cases of clinical infection and fifty-seven staphylococcus positive stools. Fifteen months later there were seven cases of infection and one staphylococcus positive stool in an



equivalent population. It therefore appeared that the program was having some influence on the reduction in the number of cases of all types of clinical infection and likewise on the reduction of bacterial pathogens present as observed in the stools. The average case rate and the average positive stool rate have remained at a very low level up to the present time. No cases of epidemic diarrhea of the newborn were observed over the four year test period nor were any cases of *Salmonella* or *Shigella* infection observed. The type of impetigo now present is markedly different than that seen at the beginning of the four year period. Four years ago, an infant with impetigo would generally be covered with lesions. At the present time the vast majority of infants classified as cases of impetigo have only a small number of lesions, usually localized in one skin area. There has been a general decline in all of the types of nursery infection ordinarily observed. This four year freedom from the diarrheal diseases seems rather remarkable in view of the fact that this nursery had experienced three consecutive outbreaks of epidemic diarrhea of the newborn in the three years prior to the beginning of the study. On the basis of this four year experience it seems possible to draw certain tentative conclusions. These are:

1 It is possible to establish a workable pattern of technique which has as its objective the reduction or elimination of nursery infection.

2 This technique appears to be responsible for the reduction in the incidence of neonatal diarrhea and the reduction in the incidence of other nursery infections.

3 *This technique also appears to be responsible for a reduction in the incidence of pathogenic bacteria observed in the stools of normal infants.*

No attempt has been made as yet to evaluate individual nursery procedures in relation to infection control. It is felt, however, that the more important procedures are:

- 1 Expert supervision
- 2 Adequate personnel
- 3 Infection control in nurses and mothers
- 4 Carrier control in nurses and mothers
- 5 Sterilization of formulas
- 6 Rigid isolation of infected cases
- 7 Hygiene technique

### Epidemic Diarrhea of the Newborn as a Hospital Problem

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The main consideration in the construction of a new nursery or the reconstruction of an old one is efficiency, which may be achieved through the most economical use of the space for the best care of the infants and for minimal effort on the attendants' parts. This latter must be calculated in total effort and so the reduction of the total labor implies reduction in the number of attendants. The arrangement of the devices to be employed in the infants' care is important to save unnecessary labor and to obtain the optimal division of that labor. That is, a nurse should have duties which only a nurse can perform and not be forced to perform many small chores which an untrained person can do as well, but which cannot be assigned to the unskilled because of the nursery layout. Freeing the nurse from menial tasks should be an objective in all nursery design, for the nearer this ideal is approached the higher the level of infant care.

Another important point in nursery design is the reduction of the number of people who must have access to the nursery. As far as possible, the nurses on duty should be the only ones to have access to this room. Attending physicians should enter for emergency purposes only and routine examinations should be conducted in an examining room to which the patient is brought. Before entering this room the physician should scrub thoroughly at the nurses' station after hanging his overcoat and hat and preferably his suit coat and vest on hooks provided outside the nursery station. Autoclaved mask, cap and gown are donned,

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and then the doctor may go into the examining room which is guarded by an ultraviolet light curtain as well as by doors. Incidentally, all the doors to this room should swing inward so that the opening of one forces the others to close. When he has completed his examination he returns to the outside before removing his gown, mask, and cap.

The examining room can be an alcove in an entrance anteroom. Its doors serve to block free air passage from the rest of the hospital to the nursery and are protected by light barriers. No other entrance need be provided. The second door can open directly into the nursery and a third opposite the second, directly into the utility room. All service facilities for the nursery are conducted from the outside corridor by means of the utility room, which will be discussed later.

The most desirable nursery is one which is cubicled with 7 ft. walls, largely of glass. In each cubicle is the equipment to be used for that infant. This includes a nurse's gown. In the nursery there is no desk, as the charting desk is in the nurses' station outside the entrance where the nurses can sit charting while watching the infants through a large glass panel. Opposite the cubicles is a small wash basin with foot controls, the only other article of equipment in this room. The temperature should be held between 70 and 75 degrees F. and the humidity between 30 and 50 R. H. In a nursery it is preferable to sterilize the air with a glycol vapor which renders the air bactericidal and permeates the entire nursery suite. The floor is of composition, either of the type which is laid in place or that which is poured like concrete. The ceiling is of sound-deadening material and is in soft color contrast with two-tone walls. In such a quiet nursery of soft colors and diffuse lighting, fatigue and nervous tension can be reduced.

Temperature, humidity, and ventilation must be regarded seriously for the health of the infants and the efficiency of the nurses. Wide differences of opinion exist on temperature and humidity. English nurseries, according to a survey in the *Lancet* (August, 1946), are considered too hot if they are above 60° F., while the tendency in the United States is to subject infants and nurses alike to 75° or more. It is common practice in this country to maintain the temperature of the newborn nursery around 85° F. This is true even when certain infants are kept in individually heated beds. These high temperatures have an enervating effect upon the nurses and are insufficiently high for the infants themselves. It is obviously more desirable to regulate the environmental conditions of these two groups independently of each other and means of accomplishing this will be discussed later. In nurseries where there are well, full-term infants only it is unnecessary to maintain uncomfortably high temperatures.

At this point it might be well to consider the complete elimination of the private newborn nursery, because this type of nursery is more open to the introduction of infections due to the larger number of individuals who have access to it. Any member of the obstetrical staff or pediatric staff may have private patients here and each infant may have his own private nurse. Ideally, each private newborn infant would be kept in a sound-dampened cubicle attached to his mother's room. This would insure complete segregation of all infants from each other and minimize the possibilities of cross-infection.

Since this ultimate ideal is not practicable in most hospitals, the second best choice seems to be a cubicled nursery such as described before, where each cubicle functions as an independent unit with bathing facilities and the individual supplies for each infant in his own cubicle.

Since it is nearly always necessary to compromise between the ideal and the practical, a utility room in which scrupulous technique is maintained should be considered for use in nurseries where no infections exist. This room should be adjacent to the nursery and separated from it by doors and ultraviolet light barriers. Into it, autoclaved linens are passed through a small window from the corridor to the linen shelf in the room. They are received, sorted, and stored in wall cabinets here. Along the same wall but separated by a glass partition soiled diapers are rinsed and dropped into a closed hamper which can be emptied from the corridor only. Against another wall stands a long infant wash table and scales.

These are separated from the clean linen shelves by a partial barrier of glass which is desirable only to prevent splashing. The linen inlet window should not be opened, of course, when an infant is in this section of the nursery. Along the wall at the end of the room lies a large sink with a left-side drainboard. Here the used formula bottles are cleaned and set into a sterilizer or pasteurizer to the right of the sink. This sterilizer extends through the wall under a large glass window into the sterile room of the formula preparation apartment, and it is in this sterile room that the sterilizer is controlled.

The formula preparation apartment is composed of two rooms. In the first is a door to the corridor and a window at table level, similar to that of the utility room's for admitting linens, cans, bottles, and other supplies. Dr. Weymuller believes that this receiving door should be a pasteurizer to prevent bacteria coming in on the supplies. Below it lies a small door for the removal of empty cans and the like to the corridor. Inside is a sink and cabinets for storage purposes. Separating this room from the sterile room, the first room beyond, is a swinging door guarded by an ultraviolet curtain. In the sterile room is the other end of the sterilizer mentioned above, the mixing table, a hot plate, a wash basin, and a telephone. There is no door to the nursery but large glass panels allow free view of it from two sides. Here the bottles, nipples and caps are received, sterile, from the utility room, and here the formulas are prepared. When each is bottled, and the nipple in place, it is capped with a metal or glass cap and returned to the sterilizer. After sterilization the formula is removed by the nursery nurse and stored in a refrigerator in the nursery.

Such a milk room arrangement could serve any type of nursery. The nurseries themselves, however, must be modified somewhat for specific purposes. Nurseries for private and ward newborn infants can follow much the described plan. Isolation nurseries, though, are usually set up along more rigid lines, by the isolating of sick infants in separate rooms with special nurses who do not attend other babies. In most hospitals this is the only solution to the problem of isolation. It is expensive in personnel, labor, and space. On this account the suggested alternative plan may be considered.

It is possible to separate infants completely in the same room by keeping them in separate sealed compartments. Air to each of these compartments is brought from out-of-doors where no pathogens exist, and is exhausted there separately. Feedings, linens, and other necessities reach the infant through a small airlock. This is a boxlike section with a door to the inside and one to the out, only one of which is opened at a time. The nurse reaches the child through sleeves on the front of the cabinet and can view him at all times through its glass windowed top. Batteries of such cubicles can be maintained at a common temperature and humidity by a single power-unit. In such a cubicle the infant is in out-of-doors air and is unexposed to air-borne bacteria. By being so enclosed he is guarded from droplet infection to which an attendant might expose him unwittingly. His exposure to contact infection is limited to the nurse's scrubbed hands. His protection against infection is greater in such a compartment than in a separate room, and the space and personnel advantages of such an arrangement are obvious.

Premature nurseries have all the requirements of isolation nurseries plus certain special ones of their own. Here the same careful isolation technique must be maintained, the infant must be protected from the same routes of infection (contact, droplet and air-borne). Additionally, each infant has definite and individual temperature and humidity requirements while these in isolation nurseries are the same for all. In general, the smaller the premature infant, the higher the environmental temperature required to maintain his body temperature at normal and the humidity in his environmental air affects his temperature requirements directly. For example, an infant of 2 to 2½ pounds may require 96° F. of dry air to keep his temperature at 98.6° F., while in humidities of 75 plus per cent R. H. he may have a normal body temperature in 90° F. air. Additionally, infants of 4 pounds and over suffer in the excessive humidities in which those smaller ones thrive, although most infants require supplemental heat until they reach 5 pounds. Thus the selection of the temperature and humidity for each infant must be done individually. Nurses in their masks, caps and gowns suffer even from the heat required by the larger of these infants. As this is the case, it

seems logical to allow the room to be at a temperature in which the nurse is comfortable and to have each infant in an incubator where the temperature and humidity can be optimal for him.

Incubators which depend upon convection currents for drawing in the air to the infant usually draw this air from near the floor. When these are in use, specially careful measures must be employed to minimize the number of bacteria in the air. Masks on the nurses and staff help to reduce the number of these bacteria, but as the air penetrates the mask, bacteria can be carried in it. The real use of the mask is to prevent the fall of droplets from the mouth and nose. One of its greatest disadvantages is in the discomfort it produces with the consequent inclination on the wearer's part to adjust it with the fingers. This changes the route of contamination to one of contact with the bacteria, but strict self-discipline can probably minimize this. However, it does seem safest to care for the infant in such an apparatus as was described for isolation rooms and which has, in addition, temperature and humidity control and regulation.

To conclude then, nursery design should consider all measures for the safety of the infant and the comfort and convenience of the nurse as means toward the same end.

### CONCLUSION

DR. CLIFFORD.—The preceding discussion demonstrates that there is no justification for a fatalistic attitude concerning the problem of diarrhea in newborn infants.

Most of the outbreaks are the result of plain, common, ordinary "filth." It is shocking to hear of contaminated common thermometers, formulas, nipples, examining instruments, nursery basins, enema solutions, subcutaneous saline solutions, soap solutions, sterilizing solutions for hand dips, table tops, and hand brushes in modern newborn infant nurseries. It is shocking to hear of infants infected with organisms that can originate only in the human gastrointestinal tract.

The universal adoption and enforcement of the simple and practical "Standards and Recommendations for Hospital Care of Newborn Infants (Children's Bureau publication No. 292)" would go a long way toward protecting the newborn infant from the hazards of diarrheal disease. All investigators emphasize the cardinal importance of plenty of soap and water in the prevention of infection in the nursery.

It may be that the coagulase positive staphylococcus counts on infants' stools as suggested by Cummings may prove to be a useful check on nursery technique, allowing correction prior to the outbreak of infection.

Experience has demonstrated carrier-borne infection of such importance in the etiology of newborn diarrhea that routine stool and throat cultures of nursery personnel are recommended.

True epidemic diarrhea of virus etiology may strike a nursery in spite of all known precautions. In this connection the words of Dr. Dodd are reassuring, "I have never seen a serious epidemic develop in a nursery where the babies were carefully watched by pediatricians, even though the physical facilities, except for the presence of plenty of soap and water for hand washing, were poor."

We have a very useful procedure at the Boston Lying-in Hospital that has demonstrated its ability to put the fire out at the start before a serious spread has occurred. The setup consists of a separate isolation room available for every nursery, into which any infant may be instantly transferred by the nurse in charge, without a physician's permission, at the first loose stool or other sign of infection. We have mobile nursery equipment permitting the conversion of any empty room into a temporary nursery.

If one baby in the nursery develops a diarrhea, that baby is isolated.

If two babies from a given nursery develop diarrhea, both babies are isolated and the nursery is quarantined. No new baby is admitted to that nursery until it is emptied and cleaned. All new babies are admitted to the temporary nursery.

If three babies from a given nursery should develop diarrhea, we will consider an epidemic is in progress and take the necessary steps, including the notification of the board of health.

## DISCUSSION

DR JAUDON—How is the virus infection transmitted from mother to child?

DR DODD—We do not know, but some work which I have already mentioned makes it seem possible that the child acquires infection during passage through the birth canal.

DR J E GUNDY, Rye, N Y—What about the transmission of infections to the babies by visitors?

DR CUMMINGS—Visitors are a potential source of infection to the babies by virtue of the fact that they are in contact with the mothers. Unrestricted visiting is certainly dangerous to the maternal population and, in turn, therefore, to the infant population. It is my belief that visitors should be limited to both mothers and nursery. A good rule is to limit visitors to two grandmothers and the father. In nurseries where the babies are not completely segregated from the outside personnel, visitors should be prohibited.

DR CLIFFORD—Will the Chapple compromise be satisfactory in preventing infections in the nursery?

DR CUMMINGS—I am not personally in a position to make recommendations regarding the Chapple technique. I believe, however, that this technique is one of the ways of controlling nursery infection.

DR R M KEMPTON, Saginaw, Mich—Should a potential case of diarrhea of the newborn be termed epidemic diarrhea?

DR CUMMINGS—A potential case of diarrhea of the newborn should be termed epidemic diarrhea of the newborn until an absolute diagnosis can be made. However, a potential case of diarrhea of the newborn in a nursery should, from the standpoint of the hospital administrator and the attending staff, be considered as a potential case of epidemic diarrhea of the newborn until proved otherwise.

DR KEMPTON—How many cases of the diarrhea constitute an epidemic?

DR CUMMINGS—One case of diarrhea in a nursery should raise the question of epidemic possibilities. Two or more cases of diarrhea should be considered as an epidemic until proved otherwise.

DR J C MONTGOMERY, Detroit—How difficult is it to garage in Chapple bed?

DR CHAPPLE—It is not difficult, as the infant's bed can be propped up on the catches inside, a funnel holder bracket is on the wall, and the infant himself is so easily handled.

DR C O LORIO, Baton Rouge, La—What amount of glycol is to be used?

DR CHAPPLE—Approximately one part in five million parts of air with propylene glycol—about 1<sub>40</sub> of this with triethylene.

DR JAUDON—Would it be feasible to admit newborn infants from the outside to Chapple bed?

DR CHAPPLE—We do.

DR CLIFFORD—How do you cut down the bacteria count in the air in the nursery?

DR CHAPPLE—Our nursery is in a hospital for sick children, so we use ultraviolet lights as barriers and in overhead fixtures, and we plan to evaporate propylene glycol in certain rooms.

DR J H LIDAY, Denver—What is the effect on nurses from breathing vapors of chemicals?

DR CHAPPLE—None. Dr Robertson's studies on toxicity proved this beyond a doubt. Animals were subjected to many thousandfold the concentration for many months without harm.

DR. GUNDY.—What effect have chemicals on viruses?

DR. CHAPPLE.—Dr. Robertson believes the glycols kill many viruses as readily as they kill bacteria in the air.

DR. R. E. GROSS, BOSTON.—Is it necessary to heat and humidify each isolating unit individually?

DR. CHAPPLE.—While they can be built in batteries, back currents of air require that each has its own air supply; therefore, separate heat and humidity are usually employed as well. For premature infants this is absolutely necessary but for older infants heat might not be required beyond that gained from the nursery itself.

DR. DODD.—Isn't a cooling system needed too? It would be in Cincinnati.

DR. CHAPPLE.—In the insulated chambers, a small infant generates about 8° degrees of heat. If the room temperature comes with 8° F. of that required by the infant, cooling will be necessary.

DR. CLIFFORD.—How long should each newly admitted premature be placed in the Chapple isolation unit before being admitted to the regular premature nursery?

DR. CHAPPLE.—We keep them in the units their entire stay in the premature nursery, sending them home after acclimatizing them to room conditions in the unit.

DR. BARBOUR, PEORIA, ILL.—Is there any way that the glycols may be used in the various water humidifiers?

DR. CHAPPLE.—A humidifier which generates heat will evaporate glycols.

DR. CLIFFORD.—Thirty cubic feet per baby is the ideal standard setup by the Children's Bureau in nurseries for the newborn. Would not the Chapple unit be a good compromise with the Children's Bureau standard?

DR. CHAPPLE.—While I cannot answer for the Children's Bureau it would seem that it might be, as the air in the isolation unit is more free of pathogens and the baby has more fresh air in this greater volume.

DR. CLIFFORD.—What method is used for getting the glycols out into the nursery?

DR. CHAPPLE.—There are evaporating devices on the market, but any heat source such as a hot plate will serve. The glycol should be dripped from a burette at the rate required.

DR. GUNDY.—How many cubic centimeters should be evaporated per cubic foot?

DR. CHAPPLE.—Approximately .01 c.c. of propylene glycol and .001 c.c. of triethylene continuously.

DR. CLIFFORD.—Will the vapor condense noticeably or harmfully on the draperies or furniture?

DR. CHAPPLE.—It does condense on windows and doorknobs quite readily but not on draperies or furniture.

DR. B. HOYER, CINCINNATI.—What are the advantages of curtain irradiation at the door over overhead irradiation?

DR. CHAPPLE.—For most applications, the overhead method is the one of choice. When curtain irradiation across a doorway is used, it is to prevent the free passage of bacteria into or out of the space so protected.

DR. R. G. ALEMAN, NEW ORLEANS.—What about the transmission of heat from the ultraviolet lights?

DR. CHAPPLE.—It is not greater than from other 30 and 60 watt bulbs and so under most conditions is negligible. It does, however, exert some favorable effect on the circulation of air past the light.

DR. DODD.—What about the problem of getting the breast-fed baby out to his mother and back to the nursery without becoming infected?

DR. CHAPPLE.—Ideally he probably should be in the room with his mother, but if he is not he should be wrapped in a sterile sheet and conveyed by a nurse in a sterile gown who is masked and has freshly scrubbed hands.

## Round Table Discussion on Tumors, Benign and Malignant

CHAIRMAN: HAROLD W. DARGEON, M.D., NEW YORK, N. Y.

ASSOCIATES: PAUL E. STEINER, M.D., CHICAGO, ILL.

RALPH E. HERENDEN, M.D., NEW YORK, N. Y.

PAUL C. BUCY, M.D., CHICAGO, ILL.

JOHN H. DALE, JR., M.D., NEW YORK, N. Y.

HAROLD L. TEMPLE, M.D., NEW YORK, N. Y.

STUART N. ROWE, M.D., PITTSBURGH, PA.

SECRETARIES: JOHN A. BIGLER, M.D., HIGHLAND PARK, ILL.

EMELIE M. PERKINS, M.D., RUTLAND, VERMONT

CHAIRMAN DARGEON.—The title of our Round Table discussion, which is "Tumors, Benign and Malignant," requires clarification. It is not our purpose to consider benign and malignant tumors as two different, although related, groups of diseases, some of which may be fatal and others nonfatal. They will be reviewed rather as one entity; that is, the neoplastic process, whose manifestations may be quite variable but whose essential nature is similar in whatever form it occurs. From the pathological, clinical, and public health standpoints this approach is justified.

1. *From the pathological:* The problem to the student of childhood neoplasms is not alone the histologic diagnosis of the tumor but the recognition of the possible future effects of the anatomical and physiological changes of the growing child upon that tumor. That the growth process produces alteration in the tumors of children is suggested by the changes observed in such neoplasms as melanoma and neurofibroma. These may be benign initially, yet as age advances a certain number will become malignant. It is possible to determine the structure of most tumors by histologic study and, therefore, in many cases to predict the eventual course of the disease. Not infrequently, however, although the identification of the tumor may be made accurately, the future course in the individual patient may only be surmised.

2. *From the clinical standpoint:* The clinical appraisal of any disease requires a careful determination of the prognosis. Some benign tumors may be fatal. The difference between a benign and malignant neoplasm from the prognostic standpoint is often an academic one. To the individual patient the importance of the disease is not its name nor its statistical significance but whether or not he will recover from it.

3. *From the public health standpoint:* Our terms should be considered from the viewpoint of the entire childhood cancer control program. This necessarily concerns itself with lay education. Although physicians know that some benign tumors are incompatible with life, the word benign may suggest to the layman a security which is relatively or even absolutely unjustified. The word malignant, however, indicates to many people a hopeless disease. Hence, on the one hand we observe children with advanced disease who have not had a tumor treated because it was always considered harmless and, on the other hand, we see fatal cases in whom no therapy was attempted because the outcome was considered hopeless from the very beginning. It is preferable to consider all neoplasms as actually or potentially malignant and to use the word cancer in its broad meaning to include all tumors.

Tumors are observed infrequently in practice or in general hospital services; nevertheless, the very high cancer death rate places it in a conspicuous position among the causes of childhood mortality. A particularly unfortunate situation occurs in the ages from 1 to 4 years. In this age group, malignant tumors which are known to be curable in some instances, retinoblastoma, Wilms' tumors, and some somatic sarcomas, to name but a few, seem to occur more often than at other ages. In addition, a number of benign tumors, e.g., hemangiomas, lymphangiomas, ganglioneuromas, and neurofibromas, which are potentially

fatal, are observed before the fifth year. This age group, the preschool group, is not as well supervised medically as is the infant in his first year, or the school child from 6 years of age onward. Therefore, in an age group in which cancers with a not universally unfavorable prognosis occur, the unrecognized disease progresses because of lack of examination.

As would be expected from a disease which affects so many different parts of the body, the symptoms are multiple and varied. Yet the objective and subjective signs of all these neoplasms may be briefly summarized as: first, the unusual child, and second, the atypical case.

The child who shows significant differences—physically or mentally—from his fellows may have cancer. The child whose history is that of a “changed” person in that his present disorder has produced noticeable deviation from his usual mental or physical state may have cancer. The child who has a disease which appears to be diagnosed accurately initially but nevertheless runs an atypical course particularly of a chronic nature or with periodic recurrence may have cancer. I believe the various diagnostic signs which will be discussed this morning can be considered under the classifications, the unusual child or the atypical case.

The following outline indicates the essential facts which are pertinent to the diagnosis of any type of childhood cancer.

#### *Diagnosis of Childhood Cancer*

- I. Sites affected—six main body areas
- II. Varying ages of occurrence of different types of cancer
- III. Suggestive clinical observations applicable to many types
- IV. Special clinical features of individual type

This series of 1,770 cases includes those from Memorial Hospital. Several series have been added together in an effort to attain a closer approximation of the actual situation pertaining to topographical distribution than might be suggested by a single series.

#### TOPOGRAPHICAL DISTRIBUTION OF 1,770 CASES OF CHILDREN'S CANCER FROM SEVEN REPORTED SERIES

C.N.S.	Bones	Eye	G.U.	Lymph.	P.Sar.	Pharynx	Skin
370	365	235	230	204	144	36	31
Abd.	G.I.	Gyn.	Liver	Misc.	Sal.	Lung	Pancreas
19	21	25	13	18	7	5	2

The topographical distribution of 573 cases of childhood cancer observed at Memorial Hospital was as follows:

#### TOPOGRAPHICAL DISTRIBUTION OF 573 CASES OF CHILDHOOD CANCER, CHILDREN'S DEPARTMENT, 1917-1946

C.N.S.	Bones	Eye & Orbit	G. U.	Lymph.	P. Sar.
12	36	25	22	8	37
	79	15	17	33	41
	55	31	24	61	58
Total	174	71	63	104	131
Pharynx	Skin	Gyn.	Misc.	Sal.	Lip.
9	4	1	0	0	0
14	2	6	5	4	2
4	1	4	0	2	0
Total	27	11	5	6	2

There are six main body areas in which cancers commonly occur during childhood. They are the central nervous system, bones, eye, kidney, blood and lymphoid system, and skin and supporting tissues. This is of no importance to the patient if his disease happens to be located elsewhere but it has several points of importance in the over-all consideration of cancer diagnosis.



1 In attempting to diagnose a neoplastic disease in a child, the common cancers of the adult, namely those of the mouth, stomach, intestine, prostate, breast, and female genitalia, do not usually enter into the problem

2 The cancers of children, with the exception of those of the central nervous system and some lymphomas, are readily accessible to examination. Thus a diagnosis may be frequently made on physical examination alone.

3 This accessibility also increases the feasibility of therapy.

THE MORTALITY INCIDENCE FROM NEOPLASMS IN THE UNITED STATES BY FIVE YEAR GROUPS BETWEEN 1939 AND 1943.

AGE GROUP	CANCER AND OTHER TUMORS	LEUCEMIA	HODGKIN'S DISEASE
Birth to 4 years	3,095	2,430	
5 to 9 years	1,982	1,168	
10 to 14 years	1,976	895	

These general findings are not limited to tumors alone, but, as is evident, may occur in other diseases, especially chronic diseases.

*Diagnosis of Childhood Cancer*

III Suggestive clinical observations

- 1 Changes in growth of (a) entire body  
(b) individual members
- 2 Changes in temperament, behavior, intelligence, disposition
- 3 Swelling (nontraumatic)
- 4 Undiagnosed disorder of short or long duration

HEMANGIOMAS

*Diagnosis*—Hemangiomas present little difficulty in diagnosis if the lesions are cutaneous.

Most subcutaneous hemangiomas must be differentiated from a large group of somatic tumors, including lymphangiomas, fibiomas, myxomas, myomas, lipomas, neuromas, and their malignant counterparts. Biopsy is frequently necessary to establish the diagnosis.

Visceral hemangiomas may produce hemorrhage into a viscus with resultant physical signs in some instances. Visceral hemangiomas seldom occur without associated cutaneous lesions. Occasionally, however, a visceral hemangioma, intracranial, intrathoracic, osseous, which may be of serious consequence, will be present, and no external evidence of the disease will be apparent.

*Management*—The pediatrician must decide whether or not treatment should be instituted, when it should begin, and what type should be employed. The decision to defer therapy is frequently made because of the consideration that spontaneous regression occurs in many hemangiomas. It is not possible to generalize about these tumors, but I believe the risks of not treating such a tumor particularly in early infancy must be carefully calculated before any recommendation is made.

The method of treatment selected depends upon the case. Cauterization with CO snow, injection of sclerosing solutions, operative intervention, and, at times, radon seeds are the most accepted methods. A decision to treat hemangiomas or any other neoplasm in children by irradiation should be reached only after the possible effects of this form of therapy have been evaluated.

LYMPHANGIOMA

The cystic variety of lymphangioma is readily recognized. The diffuse subcutaneous lesions may have the brawny consistency of an inflammatory mass or may resemble any of the soft somatic varieties of tumors described above.

Visceral lymphangiomas occur (the mesenteric cyst is an example) and must be differentiated from other masses known to occur in the body area affected.

Treatment is usually operative, but sclerosing solutions are used with some success at times.

## NEVI

*Diagnosis.*—Nevi are not, as a rule, difficult to diagnose. They include the pigmented mole or neuro nevus, the hairy mole, and the melanoma. All may be the sites of malignant melanoma in adolescence or later in life.

*Management.*—They should be removed surgically in childhood under these conditions:

1. The nevus is a true "blue black" melanoma.
2. The nevus is growing with rapidity.
3. Its location subjects it to trauma.

4. While cosmetic reasons are not always important, they have a place in some of our decisions about children. We find that although boys and girls do not seriously object to the presence of surgical scars they do resent being called "pussy cat," "mouse," or "monkey" by their associates, because of the presence of a conspicuous nevus.

## NEUROFIBROMATOSIS

*Diagnosis.*—This curious constitutional disorder is characterized by all or some of these findings: café au lait spots, subcutaneous, submucous, or visceral fibromas sometimes of great size, osseous changes, and cerebral defects. There is a marked familial incidence in this disorder. Some 12 to 15 per cent of the tumors become malignant.

*Treatment.*—Surgical excision of any mass occurring in a child who has café au lait spots or a family history of neurofibromatosis.

## RETINOBLASTOMA

This is one of the two highly malignant curable tumors observed with comparative frequency during early infancy. (The other is the Wilms' tumor of the kidney.) It seldom occurs after 5 years of age. Of forty-three cases at Memorial Hospital it was bilateral in twenty-eight (60 per cent). It arises from the granular layer of the retina, grows slowly in most instances, and produces few symptoms.

It is discovered usually by the parent who notices the peculiar "cat's eye" pupillary reflex in the affected eye. Other symptoms we have observed are: orbital bulge; conjunctival discharge and congestion; a squint; variation in the color of the pupillary reflex of gray, green, white, red, or yellow; disturbances directly related to impaired vision, crying when the unaffected eye is covered, stumbling, "clumsiness" and turning of the head to permit unaffected eye to be used.

There is usually a considerable delay before the child is treated. Of thirty-two cases in this series in which the history could be obtained, only eight were treated less than one month from onset, and six from one to three months. In eighteen children the delay was between three months and two years.

The diagnosis is made on the ophthalmoscopic findings of a gray-white mass, vascular at times, sometimes containing calcium, flecks of which appear in the vitreous in some instances. Pseudogliomas, retrolental fibroplasia, congenital glaucoma, and tunica vasculosa lentis must be considered in the differential diagnosis.

If uncontrolled, metastases to bones, lymph nodes, subcutaneous areas, and viscera may occur.

The treatment is enucleation of the affected eye in unilateral cases. If tumors are found in both eyes, the more seriously affected eye is enucleated. Removal of the other eye may be considered, but under the method of high voltage radiation, as outlined by Martin and Reese, the preservation of sight and destruction of the tumor may be expected in some of these cases.

The familial incidence of this tumor has been known for some years. This was also the case in two families in this series.

## NEUROBLASTOMA

This tumor may occur at any age in childhood but its greatest frequency in our experience is during the first five years of life.

It arises from the sympathetic neuroblast and the primary lesion may occur in various localities. The adrenal medulla is probably the most common primary site. It may also occur in the celiac plexus, the cervical, thoracic, sympathetic and intracranial as well as in the peripheral nerves.

The course is moderate to extensive local spread and metastases to liver, lymph nodes, and bones; particularly the skull. It is an embryonal type of tumor and may mature into a benign ganglioneuroma in rare instances. It may also develop into a chromaffinoma, a tumor associated with considerable vasomotor disturbances.

An early diagnosis is difficult and is finally made only on biopsy. Its presence must be suspected in the diagnosis of abdominal and intrathoracic masses as well as by lymphadenopathy. Unfortunately the earliest indications of this cancer in many cases are the skull metastases, which appear about the orbital and auricular areas as well as the skull vault.

Treatment is by removal, when possible, and otherwise by irradiation.

#### LYMPHOID STRUCTURES AND BLOOD-FORMING ORGANS

The diagnosis of leucemia requires no discussion in this group. The diagnosis of Hodgkin's disease and lymphosarcoma may be made positively only by aspiration or formal biopsy.

Inasmuch as these cancers may affect a great variety of tissues, their clinical evidences may be few or many as well as quite varied.

*Management.*—A lymphosarcoma, if localized, should be excised if its situation makes this feasible. Hodgkin's disease and inoperable lymphosarcomas are treated with irradiation.

The leucemias in children are not irradiated. We have used urethane (ethyl carbamate) in three cases of myeloid leucemia in children.

The nitrogen mustards ( $\text{HN}_2$ : Di-beta-chlorethylamine and  $\text{HN}_2$  Tri-beta-chlorethylamine) in use up to 1946 were not effective in leucemia. Another compound of this group has been used on three children (see accompanying tables) and the decline in the total white counts has been constant enough to recommend further study. It appears that this compound has some palliative effect, the extent of which cannot be appraised at this time.

#### WILMS' TUMOR

*Diagnosis.*—The subjective symptoms of this tumor do not begin until the disease has progressed. The earliest diagnostic sign is usually that of an abdominal mass in the upper quadrant or in the flank.

It is to be differentiated from other intra-abdominal and renal tumors, splenomegalies, hepatomegalies and some inflammatory processes, notably tuberculous peritonitis.

The intravenous and retrograde pyelogram show alterations in size, position, and configuration of the kidney, pelvis and calyces.

A positive diagnosis may be made only at operation, although a presumptive diagnosis is possible in almost all cases by clinical findings. A biopsy should never be performed inasmuch as the tumor is usually well localized (some believe encapsulated) in the kidney and biopsy may produce spread regionally and systemically.

*Management.*—Surgical removal is recommended as early as possible. Irradiation preoperatively is advocated by some surgeons, particularly if the mass is extremely large. Postoperative irradiation has been advocated by many. I feel that the problem of the individual case must determine the course to pursue.

#### CONCLUDING REMARKS

It is evident that we are faced with a formidable task in our efforts to reduce the number of deaths among children from neoplasms.

While we must await further discoveries in the research fields before cancer will be completely conquered, there are some simple and obvious policies which, if now adopted, would be of immediate benefit.

*From the layman's standpoint:* (1) The public must know that these diseases constitute a very real hazard during childhood. (2) The great importance of continuing the periodic medical examination of the child which this and other medical societies have long

S. K., FEMALE, AGED 4 YEARS. BORN 2/19/43. ADM. NOV. 8, 1946. WEIGHT 39 LB.

BLOOD FINDINGS							
	10/23/46	10/24/46	10/28/46	11/11/46	11/29/46	12/23/46	1/17/47
WBC	450,000	450,000	434,000	360,000	80,000	3.8	13.2
M. Blast.	1						
Mcytes.	33	36	40		51		2
Meta.	10	8	8				2
Nonseg.	30	30	42				7
Seg.	30	30	8				56
L-cytes			1.5		1		26
Prothr.	100%						
Plate.	145						
Hgb.		8.5		7.7	8.4	10.2	11.6
RBC							4.3
Eosin.		1			3		2.0
URETH.		Dose		Dose	Dose		
		.9		1.8	2.0		

## Sternal Marrow

Total Nucl.	566,000
Megak.	11
M. Blast.	1.0
Myelocyt.	41.5
Meta.	7.5
Nonseg.	35.5
Seg.	11.5
Lymph.	0.5
Nu. RBC	2.5
Peroxidase pos.	93.0%

J. P., MALE, 4 MONTHS OLD. BORN 5/4/46. ADMITTED 10/7/46. WEIGHT 14 LB.

BLOOD FINDINGS					
	1/25/46	11/11/46	12/12/46	1/17/46	2/7/46
WBC	56,200	20,5	13,2	16,7	34,
M. Blast.	2%				
Mcytes.	16.5	4	1		7
Meta.		7	17	2	
Nonseg.	16	36	17	5	2
Seg.	19		30	11	29
Lympho.	46.5	43	43	40	50
Prothr.	100%				
Platel.	80,000				
RBC					
Hgb.	14.8	15.1	12.3	10.2	8.3
Eosin.				16	11
Nuc. RBC	1				
URETH.	Dose	Dose	Disct.		
	0.25	2 c.c.			

Sternal Marrow  
(10/25/46)

Total Nucl.	297,500
Megak.	0
Myelobl.	1.0
Myelocytes	48
Nonsegs.	41
Segs.	2
Lymphocytes	1.5
Nucl. RBC	6.5
Peroxidase positive	88%

E. N., FEMALE, AGED 10 YEARS. BORN 3/19/36 ADM. 8/22/46. WEIGHT ?

BLOOD FINDINGS				
	8/22/46	8/28/46	8/30/46	9/16/46
WBC	30 0	15 0	12 4	8 6
Blasts unidentified	35			
Baso.		14	47	
Mono		51	51	
Lymph.	65	1	1	
Segs.			1	
Nonsegs				
Hgd	13 7	10 2	11 6	73%
RBC	Mod ach	3 8		

URET <sup>†</sup>	Dose 1 gm t i d.
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Sternal Marrow	
P	1
Stab	2
Ly.	22
Early blasts	59
Metas	3
Blast.	13
Nr	2% (late)

advocated not only during but following infancy cannot be overemphasized. (3) Cancer should be made a reportable disease. Our mortality statistics are relatively satisfactory but the morbidity rates, certainly among children, are not.

*From the physician's standpoint:* (1) A revision in our approach to the differential diagnosis of swellings, obscure symptoms, and physical and psychological peculiarities would seem indicated by the study of the histories in a comparatively large series of children's cancers. Neoplasms must occupy a primary position in the consideration of any of these conditions, not because of frequency but because of the risk involved if the disease is overlooked. (2) The necessity of a prompt and thorough investigation of any suspicious masses or symptom complex is evident. (3) The early and more general use of the aspiration biopsy is advocated. (4) We must appreciate that there is no such thing as an early diagnosis of childhood cancer. Although we may be able to diagnose the disease soon after the onset of symptoms, the life of the tumor may antedate a diagnosis by months or years.

The collaboration of the parent, physician, surgeon, pathologist, roentgenologist, radiologist, and health officer is necessary in each case of childhood cancer if unnecessary deaths from this group of diseases are to be prevented.

### The Radiological Aspects of Benign and Malignant Tumors in Infants and Children

John H. Dale, Jr., M.D., New York

In a general pediatric service, the incidence of benign and malignant tumors in infancy and childhood, excluding hemangiomas and the lymphoblastoma group, is low in proportion to other conditions. Conversely, the mortality rate of the malignant group and of some of the benign group equals or surpasses that of the more common diseases. This has been true in our experience at the Children's Clinic of The New York Hospital during the past fifteen years.

It has been our experience that the radiologist is seldom called upon to examine those patients in whom the tumors are so located that the diagnosis is readily afforded, either through a physical examination or through tissue study subsequent to biopsy of the tumor. Consequently, our records reveal few examples of the somatic soft tissue tumors, such as lipomas, neurofibromas, neurosarcomas, and cutaneous hemangiomas.

Excluding tumors of the central nervous system, the most common locations of the benign and malignant tumors, from the radiological point of view, have been the skeletal system, the kidney and the adrenal glands, and the mediastinum.

In the skeletal system, the most frequent benign tumors have been those classified as the benign osteogenic tumors. These arise from bone and/or cartilage, and include the osteomas and the osteochondromas or exostoses.

The osteoma arises from the unbroken cortex of the bone and appears radiologically as a rather well-circumscribed outgrowth of bone. This tumor is usually found between the ages of 8 and 19 years. It grows slowly and does not become malignant. The flat type is the most frequently described form.

The osteochondroma arises from the shaft of the bone in the vicinity of the attachment of tendons, hence the most common location is at the end of the shaft near the joint. Two forms are usually seen: the flat and the pedunculated. In both, the bony base is covered with a cartilaginous cap which imparts the irregular outline and the radiolucent areas seen on the x-ray film. Both arise from the unbroken cortex and the shaft is generally thickened at the site of the tumor. The direction of growth of the pedunculated type is that of the greatest muscular pull. There is often a clear demarcation between the bony base and the cartilaginous cap. Both forms may undergo malignant degeneration and give rise to secondary chondrosarcomas which are highly malignant and resistant to irradiation therapy. This change is rare in childhood and usually occurs after puberty.

In searching the files for examples of the nonosteogenic type of tumor in the age group represented in the Children's Clinic, I was unable to find any cases of the more common bone cysts and benign giant cell tumors. The examples of these lesions are taken from the pediatric service of the Memorial Hospital, which maintains an active tumor service.

Bone cysts are localized, fibrocystic, destructive lesions with no power of bone formation. They are almost always found under the age of 15 years. The most frequent sites are in the metaphyses of the proximal ends of the femurs, tibiae, and the humeri. Radiologically, they appear as well-defined, radiolucent areas. The medullary cavity is dilated, and the cortex is eroded and thinned from the inside. The normal bone markings in the area of the lesion are destroyed and the cyst may present a multilocular appearance. In contrast to the giant cell tumors, the bone cyst is limited to the shaft side of the epiphyseal line and does not involve the epiphysis. The cortex is intact but is sometimes ruptured if the tumor grows to an excessive size. Pathological fractures occur at the site of the cysts and lead to a reparative periosteal reaction. Enchondromas are identical in their radiological appearance but they are usually limited to the small bones of the hands and feet or to the vertebral bodies or sternum. Myelomas are found in the same locations as cysts, but they are vaguely outlined and destroy the cortex without expanding the medullary cavity. This type of tumor is rare in childhood. Solitary abscesses may be confused with bone cysts. The former are almost always found in the proximal end of the tibia.

The giant cell tumor of bone resembles the bone cyst and is found in the same anatomical sites as well as in the distal ends of the radii and femurs. It has been stated by Geschickter that 90 per cent of the tumors of the distal end of the radius are giant cell tumors. The tumor is rare in childhood. As the slide illustrates, the main point of differentiation from the bone cyst lies in the fact that the giant cell tumor is not limited to the shaft side of the epiphyseal line and tends to involve the epiphysis as well as the spongiosa of the metaphysis. The medullary cavity is expanded and the cortex is thinned and ruptured from the inside as in the bone cyst. Since the tumor has no power of bone formation, no new bone is seen except the reparative periosteal reaction, which follows pathologic fracture through the site of the lesion. A small percentage of giant cell tumors undergo malignant change. In contrast to bone cysts, the giant cell tumor does respond to irradiation therapy.

Bucy and Capp, in 1930, reported on primary hemangiomas of bone. They described the radiological findings of the lesion in the tubular and the flat bone. We have seen very few involving either type of bone. The intraosseous hemangioma of tubular bone is well demonstrated in the next slide. The involved metacarpal bone shows a central, expansive type of lesion with a peculiar multiloculated or soap-bubble appearance. The cortex is thinned and the medullary cavity is dilated. There is no periosteal reaction, such as has been

described by Sherman in a similar tumor of the femur of a 2½-year-old girl. The soft tissues of the third finger are hypertrophied and clinically this finger was involved by a cavernous type of hemangioma.

In the vertebrae, the hemangiomas are recognized radiologically by the thickening of the vertical trabeculae. These lesions are said to occur in about 11 per cent of autopsies and often remain silent during the life of the individual.

In the flat bones, the picture is different and characteristic. Here one sees a sunburst radiation of trabecular markings radiating from a common center. The periosteum remains intact but may be elevated.

Malignant osteogenic tumors of the bone are rare in infants and children. In the past fifteen years we have had 16,800 admissions under the age of 13 years, and we have not had a case of osteogenic sarcoma.

The osteogenic tumors are most common during puberty. They usually occur in the long bones near the epiphyseal line. They are rare in the center of the shaft. The osteoblastic type occurs most frequently in the humerus, femur, and the tibia about the age of puberty. The early radiological signs are an increased density or sclerosis of the medullary cavity and a periosteal thickening. After the tumor has broken through the periosteum and invaded the soft tissue, the characteristic sun-ray radiation of spicules perpendicular to the shaft of the bone are seen. These radiate into the soft tissue tumor mass. There is little visualized destruction of the bone, as can be seen on the slide. The radiation is well demonstrated, as is the increased density and the small amount of cortical destruction.

The osteolytic type causes no widening of the shaft as was seen in the osteoblastic type and no new bone formation in the form of spicules is seen. There is marked destruction of the medullary cavity and the cortex. As a rule, this type rapidly destroys the bone and invades the soft tissue early in the course. Both types of osteogenic sarcoma metastasize to the lungs and both are radioresistant.

The only nonosteogenic malignant tumor of childhood is the Ewing's endothelioma. We have had two cases in fifteen years. One was of the rib and the second of the ilium. Ewing's tumor may arise from the tubular or from the flat bones. The tumor metastasizes early, mainly to the lungs, and is very malignant. It responds well to irradiation at first, and then seems to become resistant. The initial response to irradiation may so change the cellular composition of the tumor that it becomes impossible for the pathologist to make a diagnosis. The use of the response to irradiation as a means of differential diagnosis should be evaluated with this fact in mind.

In the long bones the tumor is first seen radiologically as a thickening of the cortex and a widening of the medullary cavity, followed by a splitting or lamination of the periosteum to give an onion-skin appearance. At this stage, the radiological picture is often mistaken for osteomyelitis and it is here that biopsy is of the greatest value in establishing the true diagnosis. As the tumor progresses, there is extensive destruction of the spongiosa and the cortex, sun-ray radiation of spicules into the soft tissue mass may appear, similar to the osteoblastic type of osteogenic sarcoma, and there may be involvement of the epiphysis. Although the usual site is at the end of the long bones, the tumor may arise anywhere along the shaft and eventually involves over a third of the bone.

In the rib, as this slide demonstrates, extensive destruction is seen with the appearance of many areas of radiolucency. The mottled appearance is said to be frequently seen and often there is direct extension to the pleura with the formation of a bloody pleural exudate as is suggested in this case.

When Ewing's endothelioma arises in a flat bone, the radiological picture changes markedly. In this case, the ilium is involved. It has the appearance of increased density and sclerosis of the bone without destruction of the cortex. Close inspection of the film reveals the area to have a mottled appearance. This was called osteomyelitis until a biopsy was done and the diagnosis established. The response to irradiation was good and the bone returned toward normal, only to present a recurrence later with the development of pulmonary metastases and death in about a year.

Secondary or metastatic tumors of bone are seen with the lymphoblastoma group of tumors, with neuroblastomas of the adrenal glands, with retroperitoneal sarcomas, and very

rarely with Wilm's tumors of the kidney. The characteristics of these will be pointed out in the discussion of the primary tumors.

Excluding the lymphoblastoma group and the central nervous system tumors, the commonest malignant tumor of infants and children has been the Wilm's mixed embryonal or adenomyofibrosarcoma. Eight such patients have been diagnosed in the past fifteen years. Seven are dead and one is alive seven months after operation. Six of the eight cases occurred under the age of 5 years and, of these, five were in children under 3 years of age. The radiological examination revealed a large mass in the region of the kidney, with displacement of the renal pelvis and calyceal system of the involved side on retrograde pyelography. On intravenous pyelography, there was a failure to visualize the upper urinary tract in all of the cases in which this method was used. The same radiological picture is often seen with neuroblastomas of the adrenal gland and with retroperitoneal sarcomas. In neuroblastomas, we have found calcification in the tumor in over half of the cases. This has been reported by Bachman, Parsons, and Blatt as characteristic of this type of tumor. Neuroblastomas metastasize to bone relatively early, while Wilm's tumors rarely involve bone but tend to metastasize to the lungs. The retroperitoneal sarcomas tend to spread to the bone and into the abdominal cavity. The Wilm's tumors present a solitary or multiple nodular involvement of the lung, tending to concentrate in the lower lung fields. The multiple nodules are circular, well defined, and tend to be of the same size. This is not diagnostic, since Ewing's sarcoma and osteogenic sarcoma present the same picture, but, in the light of a tumor in the region of the kidney, the appearance of the lung metastases takes on more importance.

The next slides illustrate the commonly found tumor mass and two of the variations of the renal pelvis displacement and distortion seen as a result of the tumor growth. The degree of displacement and distortion depends upon the location of the tumor in the kidney.

The variations of the pulmonary metastases are well demonstrated in the following group of slides. The first is one of a solitary large nodule. It appears to occupy most of the right upper lobe. Clinically, it did not cause bronchial obstruction. The lack of obstructive symptoms is common in children, while in adults, obstructive signs and symptoms are often the first warnings of pulmonary metastatic involvement.

Multiple metastases tend to be discrete, of the same size, and tend to concentrate in the lower lung fields. The radiological picture, as I have stated, is not diagnostic but is very suggestive, especially with the knowledge of a mass in the kidney area or of an operation in this region.

The largest group of malignant conditions we have encountered has been the lymphoblastomas. Leucemia and Hodgkin's disease have occurred most frequently. These cannot be differentiated radiologically when they involve the mediastinal lymph nodes. In our experience, Hodgkin's disease has been the commoner in this location. The sternal marrow, peripheral blood studies, and biopsy of the superficial lymph nodes establish the diagnosis. The radiological examination merely adds confirmatory evidence. Both of the conditions may involve the mediastinal nodes and present similar pictures. Both respond well to irradiation.

The following illustrate the advanced state of Hodgkin's disease and the good response following radiation. The earlier state of the disease in the mediastinum shows the bilateral enlargement of the hilar nodes and the increased bronchovascular markings.

The acute lymphatic leucemia of childhood often shows changes in the bone on x-ray. As pointed out by Baty and Vogt, one constant finding has been the band of radiolucency proximal to the metaphysis, usually at the distal end of the femur. It may be found at the distal end of the tibia. In our series of over sixty cases, this has been a common finding. This is not pathognomonic and is found in many conditions which lead to a poor nutrition of bone. In the more advanced stages of marrow involvement and replacement, actual destruction of the bone may be seen, as illustrated in the following. Here one can see the areas of radiolucency in the metacarpals and phalanges, the osteoporosis, and the destruction of the cortex. Such a picture is seen in the neuroblastomas metastasizing from the adrenals. It is said that these metastases have a predilection for the proximal ends of the long bones, while leucemia usually is found at the distal ends. The neuroblastoma lesions have a peculiar quill-like radiation due to periosteal reaction. This is thought by Rypins to be seen most commonly in neuroblastoma. The lesions of the bone are widespread and the radiation is



perpendicular to the shaft of the bone. Leucemia very seldom shows periosteal reaction, and the lesions are not widespread as a rule.

Leucemia may sometimes invade the diploic spaces of the skull and give rise to a mottled appearance with bone destruction. The same may be seen with neuroblastoma and with lymphosarcoma.

Mediastinal tumors, other than the lymphoblastomas discussed previously, have been rare in our experience. We have seen one ganglioneuroma located in the usual position for such tumors, the posterior mediastinum. It caused its symptoms purely through pressure. The final diagnosis was made at the operation. One thymoma of the small cell sarcoma type was encountered. This was also proved at operation. The radiological pictures of these two lesions are illustrated in these last two slides.

Very occasionally we have diagnosed polypi of the large intestine by means of the barium enema and air contrast studies. Polypi have been rare in our patients. Occasionally they may become malignant, hence their recognition and removal are important. The combination of barium and air contrast studies is a helpful means of demonstrating the sessile and the pedunculated tumors of this nature, as the slide reveals.

The radiological examination is not infallible in the diagnosis of tumors of the various systems of the body, but it is of the greatest aid in the early recognition or exclusion of many of the conditions. In others it merely adds to the completeness of more obvious conditions. It should be used as much as possible and the examinations repeated if the first does not reveal the evidences of the pathology suspected. The radiological examination must be combined with the information gained by the other methods of investigation in order to be of the maximum value. In the early stages of bone tumors, the radiological changes are so slight that they may be overlooked unless the radiologist has had a wide experience in such conditions. The results of the roentgen examination should be checked by biopsy whenever possible to diagnose definitely the early tumors, since only the early recognition and treatment give hope for survival.

### Tumors of the Brain in Childhood

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- I. Metastatic tumors
- II. Infratentorial tumors
  - A. Tumors of the brain stem
  - B. Malignant tumors of the cerebellum
    - i. Medulloblastomas
    - ii. Sarcomas of the meninges
  - C. Ependymomas of the fourth ventricle
  - D. Astrocytomas of the cerebellum
- III. Supratentorial tumors
  - A. Pinal tumors
  - B. Tumors of the hypothalamus and optic chiasm
  - C. Craniopharyngiomas

Unlike tumors elsewhere in the body, tumors of the brain do not readily lend themselves to subdivision into malignant and benign types which classification is so useful with tumors in other parts of the body. Tumors of the brain present quite a different problem. In many instances they are as "malignant" as tumors elsewhere, in that they cause the death of the patient. Likewise, they invade and destroy normal tissue. But, except for those occasional tumors which have spread to the brain from other parts of the body, they do not metastasize outside of the central nervous system. It becomes necessary, therefore, to classify tumors of the brain upon a different basis. The two most important differential criteria are the growth characteristics and the sites of predilection of the different tumors.

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## METASTATIC TUMORS

*Metastatic tumors* of the brain are rare in childhood. One of the better known is the retinoblastoma of the eye which spreads to the brain as well as to other parts of the body. However, any tumor of this type is so uncommon as to merit little attention here.

Primary tumors of the brain fall naturally into two large groups. Those which appear above the tentorium cerebelli and those which develop in the cerebellar fossa. Unlike adults, children suffer frequently from tumors below the tentorium. In fact, over two-thirds of all of the tumors which occur during childhood are found in that location.

## INTRATENTORIAL TUMORS

*Infratentorial tumors* found in children fall into four definite groups. They are the tumors of the brain stem, the malignant tumors of the posterior midline of the cerebellum, astrocytomas of the cerebellum, and the ependymomas of the fourth ventricle.

*Tumors of the Brain Stem* differ in one striking way from all other common intracranial tumors in childhood; they are seldom associated with increased intracranial tension. These tumors usually arise in the pons, although occasionally the medulla oblongata or the midbrain is primarily involved. The most characteristic symptoms are the paralysis of one or more cranial nerves. The sixth or abducens nerves are most frequently affected, with a resulting paralysis of lateral movement of the eyes. However, the destruction of the facial nerve and of the motor nucleus of the fifth cranial nerve with paralysis of the muscles of the face and of mastication is not uncommon. Frequently, the ninth and tenth nerves are involved, so that the child has difficulty swallowing and talking. Sensation may occasionally be lost in the face on one side, and even more uncommonly on the opposite side of the body. Although the long fiber tracts which are concerned with sensation are not often sufficiently involved to give rise to much that is obvious on examination, the motor and cerebellar pathways are usually affected. The result is varying degrees of paralysis, disturbances of reflexes, and severe incoordination with disturbances of voluntary control of the movements of the extremities, and a marked uncertainty of station and gait. Frequently, these children suffer from severe nausea and vomiting. This difficulty plus the trouble in swallowing which affects so many of them often results in a severe loss in weight with an early emaciation.

Because the signs of increased intracranial pressure are rarely found in these children they are often misdiagnosed as suffering from an encephalitis. This error is further contributed to by the fact that these children frequently run a low-grade fever, and it is not uncommon to find a moderate increase in white cells in the spinal fluid. However, the differential diagnosis is usually made simple by a slowly progressive development which extends over a much longer period of time than one would expect of an encephalitis.

Unfortunately, there is no satisfactory treatment for tumors of this type. Most of them progress rather rapidly, although in a few instances the condition may extend over a period of years.

All of the other tumors in the posterior fossa are characterized by the signs and symptoms of increased intracranial pressure. Of these, vomiting is one of the earliest. Although projectile vomiting may occur, the vomiting may differ in no regard from that seen with gastrointestinal disturbances. It commonly occurs in the early morning shortly after arising, and even before the child has eaten. But it may occur at other times. Headache, likewise, is commonly of the early morning variety. The location of the pain is usually of little localizing significance. And in many children the discomfort of the headaches does not seem proportionate to the other symptoms. Children's heads, unlike those of adults, can expand in response to intracranial hypertension. As a result, the heads become too large for the children's caps, and on x-ray examination of the skull the sutures will be found to be widened and the bones of the skull separated. This fact is said to give rise to a peculiar note on percussion of the skull, known as Macewen's sign. This sign, however, is not a reliable one. Increased intracranial pressure also gives rise to choking of the optic discs or papilloedema. However, as such edema of the optic nerve head does not result in any

disturbance of vision until late in its course, when secondary optic atrophy has occurred, it is found only on careful and complete examination. Paralysis of one or both abducens nerves with a resulting crossing of the eyes and double vision is a not uncommon result of increased intracranial pressure and a cause of serious disturbance of the child's vision.

These symptoms of intracranial hypertension may occur with any of the intracranial tumors, or with any other condition which increases the intracranial pressure. They are, therefore, of little help in determining the nature or location of the tumor. However, each one of the tumors has clinical characteristics of its own which makes it possible to recognize the kind as well as the location of the tumor in most cases.

*Malignant Tumor of the Cerebellum* are common tumors in children. Pathologically they fall into two groups, the medulloblastomas and the sarcomas of the meninges. The *medulloblastomas* occur predominantly in boys, usually about 5 years of age. Because the posterior part of the midline of the cerebellum where they develop is part of the vestibular mechanism and is concerned with the maintenance of balance, these tumors are characterized by unsteadiness of posture and of gait. There may be little else in the way of symptomatology apart from the signs of increased intracranial pressure noted above. These are rapidly growing tumors. They tend to spread through the pathways of the cerebrospinal fluid to produce implants of tumor on the surface of the remainder of the brain and spinal cord. No tumor of this type has ever been successfully removed. They are very susceptible to x-rays. Unfortunately, this susceptibility does not persist and in the course of one to three years the tumor again begins to grow despite enormous doses of radiation and soon results in the death of the child.

*Sarcomas of the meninges* do not present such a uniform picture as do the medulloblastomas. They are most common in the posterior fossa, but may occur in the cerebrum. They may arise in the posterior midline of the cerebellum, just as the medulloblastomas do, but are also frequently found on the superior surface of one of the cerebellar hemispheres. They may occur in young boys, but they are as frequent in girls as in boys and may occur in young adults as well as in children. When they occur in the midline of the posterior part of the cerebellum of young children they do not vary greatly in their course from the situation just described with medulloblastomas. That is, they respond to the x-rays for a time, but soon run a rapidly fatal course. However, when they occur in adolescents or in young adults the outlook is often much more favorable, and with extirpation and intensive x-ray therapy some of these people have lived for many years in relatively good health.

*Ependymomas of the Fourth Ventricle* are often indistinguishable clinically from a medulloblastoma. Although they grow more slowly than do the medulloblastomas or the meningeal sarcomas and do not appear as malignant microscopically as do these other tumors, the outlook is just as unfavorable in most instances. As they lie in the fourth ventricle and compress the brainstem to a thin layer, and also as they arise from the floor of the ventricle and invade the vital tissues in that region, their complete removal is almost impossible. The mortality of operations upon this type of tumor is very high. They are not favorably influenced by x-rays.

*Astrocytomas of the Cerebellum* are fortunately the most common single type of tumor which occurs within the intracranial cavity in children. They usually arise in or near the vermis but grow laterally to involve one of the cerebellar hemispheres. Furthermore, they usually are associated with a cyst which lies within one of the cerebellar hemispheres. Because of this lateralized character of these tumors they typically produce symptoms of cerebellar dysfunction which predominantly involve the extremities on one side. These extremities are awkward or ataxic. The incoordination of the arm makes it difficult to eat and to write while the involvement of the leg causes the child to stagger and deviate toward the side of the tumor. There is usually a nystagmus of the eyes which is coarser on looking toward the side of the tumor and more rapid and fine on looking toward the other side. The extremities on the affected side are often hypotonic and the tendon reflexes may be diminished. The child's head is often tipped toward the side of the tumor. There are also the usual signs of increased intracranial tension which differ from those seen with the medulloblastoma and sarcoma only in that they usually develop somewhat more slowly.

These are among the most favorable of all tumors of the brain. They can usually be removed completely. When this can be accomplished the child usually makes a complete recovery and has no further trouble from this source. If such favorable results are to be accomplished a complete removal is essential. Evacuation of the cyst or removal of part of the tumor will not suffice. These tumors are not influenced by the x-rays.

#### SUPRATENTORIAL TUMORS

Tumors which occur above the tentorium, like those in the posterior fossa, differ widely from the tumors which occur in adults. The vast majority of tumors occurring in adults arise in the cerebral hemispheres. That is a very uncommon location for a tumor in a child, and when one does occur there it is usually a sarcoma of the meninges. Most of the tumors occurring above the tentorium lie in or near the third ventricle. Three different types form the great majority of these. They are the pineal tumors, the tumors of the hypothalamus and optic chiasm, and the craniopharyngiomas.

*Pineal Tumors*, in addition to producing the symptoms of increased intracranial pressure, give rise also to symptoms of involvement of the midbrain. The most common of these symptoms is the paralysis of conjugate upward movement of the eyes. The pupillary light reflexes may also be lost; tremor and ataxia may develop because of involvement of the superior cerebellar peduncles and the red nuclei; and there may be evidence of compression of the motor pathways in the cerebral peduncles. Many of these tumors can only be correctly localized by ventriculography. They are extremely difficult to treat surgically. For that reason it is now rather generally thought best not to attempt to remove the tumor initially. Instead, the internal hydrocephalus is first relieved either by leaving a flanged needle in place in the lateral ventricle to provide continuous drainage or a third ventriculostomy is made in order to short-circuit the obstruction of the aqueduct. Then the patient is given x-ray therapy. Many respond surprisingly well to this treatment. Should it fail, a direct surgical attack upon the tumor can be considered. However, very few such attempts to remove the tumor have ended successfully.

*Tumors of the Hypothalamus and Optic Chiasm* may involve either one of these two structures predominantly. But in most instances both are involved but to varying degrees. Tumors of the optic chiasm occur typically in individuals who are victims of von Recklinghausen's neurofibromatosis. In many instances the peripheral manifestations of this disease, which is usually hereditary, are not striking. There may be only a café au lait patch on the skin, a few subcutaneous nodules, or a tumor along one of the peripheral nerves. However, whenever an individual with neurofibromatosis begins to suffer from failing vision, a glioma of the optic chiasm is the most likely cause. In addition to impaired vision such tumors commonly produce a swelling of the optic disc and x-ray examination of the optic foramina will usually reveal a dilatation of that bony channel. There may be a defect in the visual fields but it is seldom the precise bitemporal hemianopia which is usually seen with pituitary adenomas which compress the optic chiasm. Often there is a central scotoma or an irregular defect in the visual fields. When the hypothalamus is involved the symptoms are usually drowsiness and lethargy, polyuria, polydipsia and polyphagia, adiposity, and retardation of sexual development. Many of these patients will run a low-grade fever.

Surgical treatment of these tumors is rarely satisfactory. Occasionally they respond to x-ray therapy, at least for a time, but the prognosis is always poor.

*Craniopharyngiomas* arise from embryonic remnants in the pars tuberalis of the hypophysis on the under surface of the hypothalamus in the region of the tuber cinereum. They are epithelial tumors composed of stratified squamous epithelium. The symptoms to which they give rise are the result of compression of a number of neighboring structures. Because they grow upward and occlude the third ventricle they give rise, particularly when they occur in children, to the signs of increased intracranial tension. This upward pressure also involves the hypothalamus and adiposity, polyuria, and polydipsia, and sexual retardation with atrophy results. Pressure upward and forward upon the optic nerves and chiasma produces a failure of vision and ultimate blindness. It is uncommon with craniopharyngiomas to find the sharp bitemporal defects in the visual fields which are the rule with pituitary adenomas. If the pressure downward upon the hypophysis is greater than that upward on the hypo-

thalamus, a retardation of growth with the production of a pituitary dwarf, precocious senility, and sexual retardation are the outstanding symptoms.

These tumors are microscopically benign and frequently cystic. Nevertheless, they are one of the most difficult of all neurosurgical problems. They are so closely adherent to the undersurface of the hypothalamus that a removal of the tumor without destruction of this important neural mechanism is virtually impossible. As a result these tumors are rarely cured. Evacuation of the cystic cavity may produce a remission of some of the symptoms for a variable number of years, but by and large that is all that one can hope for.

There are of course other neurosurgical lesions which one may encounter and which offer a much more hopeful outlook. There are the occasional benign removable tumors of the cerebrum, and the subdural hematomas. These must never be missed in the mistaken idea that a hopeless neoplasm is present. Cerebral abscesses, too, although now more uncommon, are much more hopeful than before the introduction of chemotherapy.

However, so far as tumors are concerned it is fairly safe to say that brain tumors in children are divisible into two groups: the astrocytomas of the cerebellum, which form about 30 per cent of the entire group and which can be successfully removed in the majority of cases with the patient permanently cured; and the other tumors of the brain, for which little can be done beyond temporary relief.

### Pathology of Benign and Malignant Tumors in Childhood

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#### I. BENIGN TUMORS

The benign tumors of childhood exhibit both quantitative and qualitative differences from those of adults; they are less numerous and the relative proportions of the various types are different. Several explanations may be used to account for these observations. They may reflect merely the slow rate of growth of a tumor so that even if it began before birth or at an early age it does not attain a noticeable size during childhood. Or it may indicate that there has not been lapse of sufficient time for accumulation of and exposure to causative factors, or for such factors to have exerted their effects on the cells through an adequate tumor induction time. Finally, origin from blastomeric inclusions must be given consideration in the mixed and teratomatous tumors, which are relatively commoner in children than in adults. The high incidence of these tumors in the newborn and during infancy and childhood, a period when rapid cell differentiation and growth are occurring, strongly suggests an etiologic relationship to some dysontogeny. If the Cohnheim theory of tumor formation from misplaced embryonal rests has any place today, it is surely in relation to these tumors.

It is difficult to determine the exact size of the problem of benign tumors in childhood because few data are available. Most reports deal only with malignant neoplasms. A few data can be culled from general papers on tumors. A study of the benign tumors found as incidental lesions at necropsy in our own material showed that such tumors are much less common in children than in adults.

Surgical material yields more information. A review was made (at the Children's Memorial Hospital, Chicago, with the kind permission of Dr. Stanley Gibson and Dr. J. P. Simonds) of over six hundred specimens removed surgically from children for diagnosis or treatment. About 22 per cent were malignant tumors which will be discussed in a later paper. About 63 per cent, or nearly two thirds of the specimens, were benign tumors with which we are here concerned. The remainder, about 15 per cent of the total, were non-neoplastic lesions about which more will also be said shortly. The latter group was of special interest because of the difficulty in separating it sharply, in some instances, from the true tumors.

On classifying the benign tumors as to type, it was found that the largest group was composed of polyps papillomas, and polypoid adenomas arising from various epithelial surfaces. Then, in descending order of frequency, the following were found: hemangiomas, dermoids and epidermoids, fibromas, lymphangiomas, nevi, teratomas, lipomas, neurofibromas,

lipofibromas, chondromas, and osteochondromas. Finally, there was a large group of miscellaneous tumors and tumorlike conditions. These, then, were the benign tumors which the pediatricians encountered most frequently.

The papillary lesions were found most often in the following locations: larynx, rectum, nose, ear, and smaller numbers in a wide variety of locations. Some of these lesions were undoubtedly inflammatory in origin and not true neoplasms as, for example, the nasal polyps. In the case of some of the others the classification is less certain. Many were undoubtedly benign epithelial tumors of adenomatous and other types.

The next largest group of benign tumors, the hemangiomas, were chiefly cutaneous. Visceral hemangiomas as, for example, cavernous hemangiomas of the liver were encountered at necropsy in children less commonly than in adults. These tumors are of special interest because their clinical behavior, which is usually benign, is unlike their histological appearance, which is often suggestive of malignancy. These tumors are composed of a plexus of blood spaces, whose structure may imitate blood vessels of any size and with varying degrees of perfection. In the simplest form they consist of endothelial-lined blood sinuses or capillaries; in their most complex form either arteries or veins may be produced. There are all grades between. These differences explain variations in color, texture, pulsation, and other clinical features. The lymphangiomas were also common. In their extreme form they become the cystic hygroma familiar to all pediatricians.

The mixed tumors formed a large series in which the structure showed increasing complexity, varying from simple epidermoids, which are cystic, through dermoids to teratoids, which may be solid. Some of the latter were malignant. It is often difficult to distinguish the benign from the malignant forms. The distribution of these tumors in the body was very wide. While a few were found in the gonads, the majority were at sites of complex embryologic development such as occurs at the poles of the body, along the spinal axis, and about the face. Their locations as well as their embryonal or complex structure, and their occurrence in young persons give support to their probable dysontogenetic nature. On the proximal, benign end of the spectrum with respect to simplicity in structure were found a number of sebaceous cysts. They are regarded by most observers as not neoplastic, but as simple cysts caused by retention of sebaceous material and desquamated cell debris. They are retained here because on the external surface of the body they can, when they are solitary, clinically resemble small dermoids and cystic teratomas.

The connective tissue tumors formed the third largest group. In descending order of frequency they were: fibromas, lipomas, neurofibromas, lipofibromas, chondromas, and osteochondromas. These tumors showed a wide anatomical distribution. The histologic appearance is indicated by their names. The diagnosis of these tumors with respect to type and degree of malignancy presents the same problems as it does at other ages.

After separating out the three main groups of tumors just enumerated, a large miscellaneous group remained. Over thirty types are represented in this group. Their distribution in the body was equally varied. They illustrate the point that although most of the benign tumors in childhood follow well-established patterns in which some tumors common in adults are poorly represented, nevertheless, sooner or later, almost every type of tumor may be encountered.

In recent years tumors which arise in the endocrine system and exert striking hormonal effects have attracted much attention. In this series such tumors formed an insignificant problem. Similarly, those types of adenomatous hyperplasia which are common in adults where they are believed to be the result of long-standing hormonal imbalances were extremely rare in children.

It may be noteworthy that with one exception the benign tumors, which are most common in adults as incidental findings at necropsy, were not seen in children at all, either in surgical or necropsy specimens. The benign tumors found in a large series of necropsies in adults included large numbers of uterine polyps and fibroids, adenomas of the thyroid, adrenal cortex, and kidney, adenomatous hyperplasia of the prostate, polyps and polypoid adenomas of the colon and stomach, hemangioma of the liver, fibroadenoma of the mammary gland, and

papilloma of the urinary bladder. Of these common types of tumors, only polyps of the colon are more than rare in children. Here is a fertile field for speculation and investigation.

The group of non-neoplastic lesions previously mentioned was of special interest. It was relatively large in proportion to the true tumors, showing that it constituted a real problem in differential diagnosis and treatment. The group is composed of lesions characterized by a mass which grossly may resemble a true tumor. It includes some cysts and pseudocysts, a few masses which are composed of heterotopic tissue and congenital malformations, and many inflammatory polyps. By their size and location these lesions may produce the same clinical effects as do benign tumors. Inasmuch as they present the same problems in clinical diagnosis as tumors, they have been retained in this material for discussion and contrast.

Just as it is sometimes difficult to draw a sharp line between hyperplasia and tumor, so also the distinction between benign and malignant tumors may be difficult. The natural history of each tumor must be known and taken into consideration in making the decision. Some cartilaginous tumors are more malignant than their histologic appearance suggests. Other tumors, including the cutaneous hemangiomas, some nevi, and others are more benign than their infiltrative nature and cell morphology indicate. There are no hard and fast rules to cover these situations; the behavior of each type must be learned.

In summary, the points are made that the benign tumors of childhood exhibit interesting and important peculiarities with respect to total incidence, types, locations, histologic diagnosis, and degree of differentiation from tumors in adults. In children, perhaps more than in adults, benign nontumorous masses exist which enter into differential diagnosis both clinically and pathologically.

## II. MALIGNANT TUMORS

The cancers of the newborn, of infants, and of children are of interest to the experimental oncologist as well as to the pediatrician. Although the incidence is lower than it is in adults, tumors at this age are not rare, and as a cause of mortality they now exceed some of the common infectious diseases. Their induction time is, of necessity, short: Whatever the cause of these tumors is, it has only a short time in which to act on normal cells to convert them to cancer cells and thus start the tumors. This alone is sufficient to set the tumors in children apart from those of adults. They are further characterized, however, by their special incidence, locations, types, behavior, and problems in diagnosis and treatment.

The natural history of some of the tumors in children is incompletely known. This is true especially for the rare types. Few physicians have occasion to see enough of them in the course of a lifetime to make adequate observations on diagnosis, course, and treatment on which final conclusions can be based. This gap should now be filled by the Children's Tumor Registry of the Academy.

*Incidence.*—To obtain an idea of the importance of cancer in childhood, the incidence must be determined. It can be expressed in a number of ways. Thus, it can be stated in terms of the entire population, children in the population, hospital admissions, total tumor deaths, hospital deaths, or necropsies.

The following analysis of incidence was made with data from three sources. These were (a) the Department of Pathology of the University of Chicago; (b) The Children's Memorial Hospital of Chicago (my grateful thanks go to Dr. Stanley Gibson and Dr. J. P. Simonds for permission to make the study); (c) the Board of Health of Chicago (these data were kindly supplied by Dr. Herman Bundesen, President of the Board of Health). The data are of different types and they supplement each other.

In the city of Chicago during 1945 there were reported fifty-one deaths from cancer (excluding neuroblastomas) in the age group of 0 to 9 years, and nineteen deaths in children aged 10 to 14 years inclusive. This constituted a tumor mortality of 12.0 per 100,000 population per year in the earlier age group and 7.7 in the older children. The actual figures are probably higher than those here given because of omission of neuroblastomas and possible other cancers, and because of the negative error in diagnosis inherent in clinical diagnosis not checked by necropsy.

At the Children's Memorial Hospital there were, over a period of years, 116 necropsies on children under 13 years of age with malignant tumors. This was 0.13 per cent of all ad-

missions, 2.49 per cent of all deaths, and 4.14 per cent of all necropsies. The per cent of deaths due to tumor was even higher in the University of Chicago series, probably because of a difference in type and selection of cases, the per cent of intracranial tumors having been higher. In 730 necropsies on children 12 years old or less there were 103 fatal tumors (14.1 per cent). In ninety-seven necropsies on children from 13 to 16 years of age inclusive, thirty (30.9 per cent) had malignant tumors. The necropsy rate at this institution averaged about 80 per cent of all deaths.

*Types.*—The cancers which occur in childhood are, in many instances, different in type from those of adults. Carcinomas are uncommon, while sarcomas as well as mixed, and embryonal tumors are common. In the combined (Children's Memorial plus University of Chicago) series of 219 malignant tumors in children aged 12 years and under, there was only one carcinoma. This was found in a liver showing juvenile cirrhosis. In adults carcinomas are about ten times as common as sarcomas.

The 116 fatal tumors in the Children's Memorial Hospital series were of the following types: Lymphatic, sixty-three (54.5 per cent); intracranial, sixteen (13.8 per cent); neuroblastoma, eight (6.9 per cent); adenomyosarcoma (Wilm's tumor), seven (6.0 per cent); sarcoma, seven (6.0 per cent); miscellaneous, fifteen (13.0 per cent). The per cent of intracranial tumors in this series was low because many cases had been referred to the University of Chicago where they helped to swell the figures for this disease.

The 103 fatal tumors in the University of Chicago series were of the following types: Intracranial, sixty-three (61.1 per cent); lymphatic, twenty-four (23.3 per cent); neuroblastomas, seven (6.8 per cent); sarcomas, four (3.9 per cent); and miscellaneous, five (4.9 per cent).

In the city of Chicago data, lymphatic tumors were most numerous. They were followed by intracranial tumors, unspecified types, and kidney tumors in that order. Thus, in these three series of tumors the order of frequency of the different types was approximately as follows: lymphatic and hemopoietic (this included leucemia, aleucemic leucemia, lymphosarcoma, and Hodgkin's disease), intracranial, neuroblastomas, renal tumors, miscellaneous sarcomas, and miscellaneous malignant mixed tumors. This is roughly in agreement with the data of others.<sup>1, 2, 3</sup>

The peculiarities of tumors in the young can be accentuated by making a special group of the congenital cases.<sup>4</sup> They can be further emphasized by comparing the cancers in two age groups namely, 1 to 12 and 13 to 16 years. When this was done with the University of Chicago material it was found that while some types (e.g., intracranial and lymphatic) persist in the older group, others (e.g. neuroblastoma) fall off. At the same time, bone tumors, chiefly Ewing's sarcoma, begin to appear. The same features were seen in the city of Chicago data where the division was made at the tenth year. Lung and other tumors appear after this age. Thus, in late childhood the change in types of tumors begins which eventually results in the pattern seen in young adults.

*Sites.*—Going hand in hand with the peculiarities in type of tumor in children are their differences with respect to location in the body. Some sites and organs which commonly give rise to tumors in children rarely do so in adults, and vice versa. Thus, in 1841, consecutive cancers encountered at necropsy at all ages but mostly in adults the order of incidence, in the ten commonest, was as follows: stomach, intracranial, colon, lymphatic, lung, mammary gland, prostate, pancreas, esophagus, and uterus. Only two of these tumors (intracranial and lymphatic) are common in childhood. The other eight are uncommon, rare, or practically nonexistent (e.g. carcinoma of the prostate). On the other hand, two of the common tumors in children, namely, the neuroblastoma of the adrenal and other sites, and the mixed embryonal tumor of the kidney (Wilm's) are common in adults, although renal carcinomas are not. Hepatoma, or hepatic cell carcinoma of the liver is the commonest carcinoma in children. It is also fairly common in adults. It is the only carcinoma with this double distinction.

*Morphology.*—Many tumors in children exhibit a dissociation between the degree of their histologic and clinical malignancy. This factor needs recognition for the correct



pathologic interpretation and treatment of these tumors. Some of them are relatively benign appearing, pathologically speaking, but are clinically highly malignant. This is true of many intracranial tumors, some chondromas, and some lymphangiomias. Some of the embryonal and teratoid tumors also fall into this category. Their cells may appear embryonal and immature but not anaplastic, yet metastases may be widespread. On the other hand a few tumors which by histologic criteria should prove to be very malignant, may have a benign course and favorable outcome. Examples of this type of behavior include the cutaneous hemangiomas, and a few of the adrenal neuroblastomas.<sup>1</sup>

#### *Special Pathology.—*

*A. Lymphatic and Hemopoietic:* The leucemias are the commonest diseases in this group. Their subclassification is dependent on cytological details and on ideas regarding nomenclature. In general it is believed that in children the blast and lymphatic forms are of relatively greater importance than the myelogenous, and that the acute cases are commoner than the chronic. Both of these observations are the reverse of the situation in adults.

Enlargement of the lymph nodes in the leucemias of childhood is often inconspicuous. This may be true both in the early and the late stages of the disease. At the same time the blood picture may be subleukemic or aleukemic. This, coupled with small lymph nodes which even on biopsy may fail to show striking changes, makes the diagnosis very difficult in such cases, a situation which rarely pertains in adults.

Hodgkin's disease was commoner than lymphosarcoma. This is a reversal of their incidence in adults. The diagnosis of these two diseases by biopsy of lymph nodes during life and by the pathologic findings at necropsy present no unusual problems.

*B. Intracranial Tumors:* The chief intracranial tumors were medulloblastomas, spongioblastomas and astrocytomas. The two former types showed a striking decrease in the 13- to 16-year age group.

*C. Neuroblastomas:* These tumors originate predominantly in the adrenal medulla but, not rarely, in other locations from nervous system elements as well. They form bulky masses in the upper abdomen signalling their presence, or they may first reveal themselves through their metastases, especially those in the skeleton. Most of them occur in the first few years of life. They bear a great clinical resemblance to the embryonal mixed tumors of the kidney (Wilm's) which also form large masses in the upper abdomen in young children. They may sometimes be differentiated by the demonstration of areas of calcification on x-ray examination. The adrenal neuroblastoma is more likely to contain areas of necrosis which calcify than is the kidney tumor. It also has a greater tendency to metastasize early and widely, but this distinction is less reliable.

*D. Adenomyosarcoma of Kidney (Wilm's):* These tumors arise from the kidney where they form large masses. They tend to grow rapidly and to metastasize widely in the abdomen and thorax. They may be congenital or appear in infancy and childhood. They are much less common after puberty. Microscopically they show a mixture of embryonal structures and tissues. Of special interest in association with their structure, age incidence, and possible etiology is the fact that some of these children exhibit developmental anomalies or defects elsewhere in the genitourinary tract.

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#### Bone Tumors

Ralph E. Herendeen, M.D., New York

Tumors of bone are often difficult to diagnose roentgenographically and even with a biopsy the prognosis must be guarded.

*Case 1.*—Benign tumor of tibia which became malignant. The radiographic diagnosis was a benign giant cell tumor. First curettage showed a benign giant cell tumor but the second curettage showed malignant changes. Even after x-ray treatment and amputation, metastasis occurred and the patient died.

*Case 2.*—Endothelioma (Ewing's sarcoma) of fibula. There was widening of the medulla and thinning of the cortex. The onionpeel appearance was not characteristic. Involvement of the soft tissues with local heat over the area was present. X-ray treatment showed a good response of the bone tumor but metastasis and death occurred.

*Case 4.*—Endothelioma of the heel diagnosed radiographically. There was good response to radiation therapy. Amputation was advised but not done. The patient is alive now, which speaks against a diagnosis of a Ewing's sarcoma. It was felt that not cutting into the tumor may have been beneficial in this case.

*Case 5.*—Fracture through a cystlike area of decreased density. Curettage showed a bone cyst lined with giant cells. X-ray therapy at first caused an increase in size of the cyst, which then later decreased in size.

*Case 6.*—Giant celled tumor of neck and shaft of femur was diagnosed radiographically. No curettage was done. It improved with x-ray therapy.

*Case 7.*—Giant celled tumor of radius. This type of tumor grows symmetrically, shows trabeculation, and extends along the shaft of the bone. In children it occurs below the epiphysis but in adults it extends into the joint. Biopsy showed a giant celled tumor. X-ray is the treatment of choice in small doses over several months.

### Intracranial Tumors in Children (abstract)

Dr. Stuart N. Rowe, Pittsburgh

Brain tumors occur in children in about one admission out of 700 in our experience on an active pediatric service in a general hospital. This is about in keeping with the experience of others. They make up approximately 17 per cent of the entire group of intracranial tumors in children and adults. The pathology of these neoplasms varies widely, but the majority are gliomas occurring in the posterior cranial fossa. Another important group are the craniopharyngiomas, growing in the suprasellar region.

The clinical picture of brain tumors is characterized primarily by symptoms of increasing intracranial pressure, including bouts of morning vomiting and morning headache, impairment of vision, and apathy and drowsiness. In some instances, slight focal neurologic changes including incoordination of hand movements and staggering gait may point to a cerebellar lesion. In the suprasellar group, endocrine changes may be apparent and x-rays frequently disclose intracranial calcification. Enlargement of the head and the positive Macewen's sign on percussion is an early and very helpful clinical finding. Changes in the optic discs varying from 1 to 6 diopters of papilledema are common. When the diagnosis is suspected, careful neurologic studies and ventriculogram are usually needed to establish the exact diagnosis and localization of the lesion. Surgical treatment is effective in the majority of patients and in a few, x-ray therapy offers marked relief over a period of months or years.

#### A. Pathology varies greatly

All malignant tumors invade, become adherent, and extend into surrounding tissues, but usually do not metastasize.

##### 1. Benign tumors

- Meningioma
- Craniopharyngioma
- Epidermoid
- Astrocytoma
- Pinealoma

##### 2. Malignant tumors

- Medulloblastoma
- Spongioblastoma
- Sarcoma

*B. Clinical picture*

It may be difficult to recognize tumors early because the child is less likely to describe symptoms accurately, is less likely to complain, and the skull is less elastic than in the adult.

## 1. Intercranial hypertension

- a. Vomiting—occurs early in the morning, is projectile, is not accompanied by much nausea, may be intermittent, lasting for three to four days at a time, and there is an absence of other gastrointestinal symptoms.
- b. Headache—not clearly defined, but usually more in the morning, associated with vomiting, and most often frontal but occasionally occipital and nuchal.
- c. Impaired vision—may extend to complete blindness. There is gradual onset, often with double vision or photophobia.
- d. Lethargy and loss of drive may be present. Mental changes may be mild.

*C. Physical findings*

## 1. Head

- a. Often enlargement of head, general or local.
- b. Veins often prominent.
- c. McEwen's sign present.
- d. Choked disc usually present, but not always.
- e. Strabismus due to involvement of sixth nerve causing paralysis of external rectus.

## 2. Focal neurologic changes

- a. Cerebellar tumors—may be no changes; usually awkwardness, stumbling, and staggering. Uncoordinated use of hands. Positive Romberg. Some myotonia, and reflexes are absent or sluggish. Usually little increase in pressure when brain-stem is involved.
- b. Supratentorial
  - (1) Craniopharyngioma—increased intracranial pressure, changes in visual fields, endocrine changes such as diabetes insipidus, and often intracranial calcifications.
  - (2) Pinealoma—endocrine changes such as precocious sexual development and impairment of eye movements.

- c. Cerebral hemisphere tumors—motor changes, speech difficulty, epilepsy, and sensory changes.

## 3. Additional diagnoses

From x-ray of the skull  
 Visual field examination  
 Spinal puncture  
 Encephalogram  
 Electroencephalogram

*D. Treatment*

Depends on pathology, location, and size of tumor. Surgery offers most cures in such tumors as astrocytomas, craniopharyngiomas, ependymomas, and meningiomas. X-ray treatment and surgical relief of pressure in medulloblastomas and spongioblastomas.

## DISCUSSION

DR. DARGEON.—I would like to ask about the terminology of benign and malignant tumors. Is there any definite criterion to differentiate the two—would it not be better to talk about benign and malignant cancer? The general practitioner may be confused with technical names of tumors.

DR. STEINER.—That would not be good because of the stigma attached to the term cancer. It would seem better to use the general term neoplasm.

DR. DARGEON.—But all tumors are not new growths.

DR. DOROTHY H. ANDERSON, NEW YORK, N. Y.—It is difficult to differentiate early neuroblastoma from leucemia. Small tumors are often not felt and one must wait for bone

metastasis. Bone marrow smears at times are difficult to differentiate into specific cell groups. Often nothing shows up in the blood stream early.

DR. STEINER.—I agree with you. Sternal punctures may be misleading.

DR. DARGEON.—One must use clinical, laboratory, and radiographic findings together for diagnosis.

DR. BIGLER.—The malignancy of lymphoma and stages up to lymphosarcoma is extremely hard to differentiate from biopsy. A tumor may appear very malignant and yet not metastasize or recur.

DR. STEINER.—Calcification occurs in neuroblastoma and not in Wilm's tumors.

DR. HERENDEEN.—I have seen calcification in Wilm's tumors, especially following radiation.

DR. DARGEON.—That may be due to hemorrhage.

DR. STEINER.—Two-thirds of fatal tumors occur in childhood.

DR. HERENDEEN.—Dr. Rowe, is there any significance in an absence or an increase in vascular marking in skull x-ray films?

DR. ROWE.—It depends upon the age of the child. They are not so pronounced until after 15 years of age. They give no significance as to the location of the tumor.

DR. DARGEON.—The diagnosis of bone tumors should not be made by x-ray alone or by test doses of x-ray. Biopsy should be done. The differentiation even then between chronic osteomyelitis and endothelioma may be exceedingly difficult.

DR. G. D. JOHNSON, SPARTANBURG, S. C.—Does treatment offer any hope for lymphoblastoma?

DR. DARGEON.—There are "five-year cures" of lymphosarcoma reported. We have one case that has survived six years. Five years is not a long enough period for a cure to be considered. The child should remain well for at least ten years. I have seen children free of symptoms of various types of cancers for seven or eight years who later succumb to the disease.

DR. BUCY.—The term "five-year cure" is merely a handle. Everyone has seen recurrence of cancer of the breast after the five-year period. In melanosarcoma we have seen metastases after twenty-five or thirty years. Five years is the arbitrary term but a useful one.

DR. STEINER.—What is the lining of the cyst which is associated with astrocytoma?

DR. BUCY.—Ordinarily it is not lined. There is a glial scar. It is important to search for the tumor when emptying the cyst.

DR. JOHNSON.—Is the earliest sign in intracranial tumors in children usually intracranial pressure?

DR. BUCY.—Usually.

DR. DARGEON.—Will you please give the differential diagnosis between lead encephalopathy and brain tumor.

DR. BUCY.—This can be very confusing. Sixty years ago the elder Dr. Bramwell said he never made the diagnosis of brain tumor without considering lead encephalopathy. In the glass and pottery industries at that time it occurred fairly frequently. It is still seen in children because they will eat anything. I have known them to lick the paint stick out of the painter's bucket. They may get it from eating painted plaster. It is sometimes acquired from using storage batteries as fuel. Toys are not often the cause now because of a change in the nature of the paint used. The chief symptoms of midline cerebellar tumors in children are staggering and increased intracranial pressure. There is marked cerebral edema in lead poisoning, which gives increased intracranial pressure, and there

often is staggering. There are two points very important in the differential diagnosis: (1) Convulsions are generally present in lead encephalopathy, rarely in brain tumors in childhood; (2) x-ray demonstration of the lead lines at the epiphyses of the long bones. These do not become demonstrable for some time after exposure. This x-ray point of differentiation cannot be used in adults. Of course, in children as well as adults there may be present other signs of anemia, stippling of the red cells, or a lead line on the gums (only found in association with carious teeth and infection around the gums). Peripheral neuritis is rare in children.

DR. DALE.—Have you seen many intracranial dermoids?

DR. BUCY.—Intracranial dermoids grow so slowly that ordinarily symptoms are not present until adolescence or adult life. Intraspinal dermoids may give rise to symptoms earlier as there is less room in the spinal canal and the spinal cord cannot adapt itself to compression as can the brain.

DR. H. S. BERMAN, DETROIT, MICH.—Do you consider encephalography dangerous if used for diagnosis when the operator is not prepared to do a trephine of the skull?

DR. BUCY.—It is not very helpful in diagnosing brain tumors in children as there is ordinarily some obstruction of the ventricular system which interferes with adequate visualization; also, it is dangerous. A child with intracranial pressure may get a herniation of the cerebellum through the foramen magnum. Even following lumbar puncture done with care and withdrawing only 5 or 10 c.c. of spinal fluid in cases of brain tumor, fatalities do occur, although they are not numerous. In encephalography, 50 or 60 c.c. of spinal fluid may be withdrawn.

DR. BERMAN.—Do not many brain tumors grow to the point where they are fatal without being diagnosed?

DR. BUCY.—Encephalography may be done in other conditions, such as atrophic lesions and a convulsive state, but not where there is reason to suspect a cerebellar tumor.

DR. BERMAN.—Do you think that many cases seen by doctors have a delayed diagnosis because of failure to do early encephalography?

DR. BUCY.—I do not think so.

DR. RUTH M. BAKWIN, NEW YORK, N. Y.—Does craniopharyngioma give any symptoms in the pharynx?

DR. BUCY.—Rarely. Several tumors, most commonly cancer, may invade the base of the skull from the nasopharynx. In a few very rare cases, craniopharyngiomas have eroded the sphenoid bone and protruded into the nasopharynx.

DR. JOHNSON.—Do you see many cases of undescended testicles which have undergone sarcomatous change?

DR. STEINER.—Changes in cryptorchidism are likely to occur later in life. The occurrence of sarcoma in testicles lying outside of the scrotum is twenty times as great as in the testicles lying in the scrotum.

#### QUESTION?

What is the prognosis in cystic hygroma?

DR. DARGEON.—The prognosis in cystic hygroma is good if operative procedures can be performed successfully. The technical difficulties may be great. It may extend well up into the neck or far down into the chest. Often surgeons have a transfusion started before operation because they do not know whether it will turn out to be a simple procedure lasting half an hour or a complicated procedure lasting two or three hours.

(Dr. Dargeon showed a picture of a retinoblastoma and stated that unilateral cases were treated by enucleation.)

DR. BUCY.—I remove the optic nerve also, as the tumor often invades the nerve.

DR. STEINER.—Do you sterilize these children? It is considered hereditary.

DR. DARGEON.—There have been cases reported where the progeny did not have it.

# Academy Proceedings

## REPORT OF THE MEETINGS OF THE EXECUTIVE BOARD OF THE AMERICAN ACADEMY OF PEDIATRICS

PITTSBURGH, PA., FEB. 23, 1947

### *Abstract of Proceedings*

A meeting of the Executive Board of the American Academy of Pediatrics was held in the Hotel William Penn, Pittsburgh, Pa., Sunday, Feb. 23, 1947. There were present Drs. Durand, Beavens, Stringfield, Hill, Kennedy, Munns, Spickard, Quillian, Bruce, Martmer and Grulee, and, by invitation, Dr. James Wilson. The meeting was called to order by the President, Dr. Jay I. Durand.

The report of the Treasurer was presented. It was moved by Dr. Stringfield, seconded, and carried that the present budget be carried over until the meeting of the Executive Committee on July 7-8.

The next order of business was the reports of Committees.

Dr. George M. Wheatley reported for the Committee on Rheumatic Fever. It was moved by Dr. Hill, seconded, and carried that the Committee consider the advisability of setting up state rheumatic fever committees to carry its objects in the various states.

Dr. James G. Hughes reported for the Committee on Cooperation with the American Legion. It was moved by Dr. Hill, seconded, and carried that Dr. Hughes be asked to keep in touch with the American Legion's (Child Welfare Division) and, in case his presence at meetings is necessary, that his expenses be paid by the Academy.

The Secretary read a letter from Dr. Harold Mitchell concerning rural school health. It was moved by Dr. Hill, seconded, and carried that the Secretary write a letter to Dr. Mitchell, stating that his report had been read with great interest, but it was the feeling of the Executive Board that before any definite action is taken, more information on the problems involved should be made available to the members of the Executive Board.

Drs. Kerlan and Stormont of the Food and Drug Administration discussed the question of cooperation with the Academy on drugs. It was moved by Dr. Kennedy, seconded, and carried that a committee be appointed by the President to cooperate with the Food and Drug Administration on problems relating to pediatrics.

The report of the Tumor Registry was presented by Dr. Harold W. Dargeon.

The Secretary read a letter from Mr. Rose of Mead Johnson and Company enclosing a check for \$25.00 for child nutrition. This money, with \$24.00 already on hand, will be allowed to accumulate.

The Secretary read a letter from Dr. Bret Ratner regarding a Committee on Allergy of the American Academy of Pediatrics. It was moved by Dr. Hill, seconded, and carried, that the Secretary inform Dr. Ratner that the Executive Board approves his idea and that he be appointed chairman of a committee to get things organized and report back at the next meeting.

The Secretary read a letter from Mr. Walter A. Taylor, Director of Department of Education and Research, the American Institute of Architects. The Secretary was instructed to write Mr. Taylor telling him the Academy would cooperate in any way possible.

Dr. Stringfield reported that he had communicated with Mr. Hutchinson concerning the National Conference on Family Life. This organization is planning a White House Conference on Child Life in 1948.

Dr. Martmer reported on the proposed library and museum of pediatrics. He showed plans of the proposed building and discussed approximate costs. It was moved by Dr. Hill, seconded, and carried that the idea of the plans be approved and the Committee continued.

Dr. Martmer read a letter from the architect who had drawn up the plans. It was moved by Dr. Stringfield, seconded, and carried that a letter of thanks be sent to the architect for what he had done, and explaining that in the event such a building is contemplated that his firm as architects and engineers will have the first consideration.

Dr. Sisson for the Committee which had been appointed to investigate and make suggestions about future policies in regard to a public relations counsel and distributed to the members a copy of the report made by Mr. John C. Gourlie, whom the Committee had interviewed.

Dr. Hubbard presented the following resolutions in recognition of the cooperation which has been received from the various organizations to make the Study at least a partial success:

*Whereas*, one year has now passed since the American Academy of Pediatrics Study of Child Health Services was launched on nationwide scale;

*Whereas*, the Academy of Pediatrics has been able to develop and conduct this Study on a much larger and more far-reaching scale than had originally been anticipated or than would have been possible without the support of the United States Public Health Service, the United States Children's Bureau, the National Foundation for Infantile Paralysis, the Field Foundation, and those commercial firms listed below;

*Whereas*, the cooperation of Academy, the United States Public Health Service, and the Children's Bureau has established an effective working relationship between two Government agencies and the Academy of Pediatrics and has set the stage upon which similar cooperation may continue in implementing the results of this factfinding Study;

*Resolved*, that the American Academy of Pediatrics express to the Surgeon General of the United States Public Health Service and to the Chief of the Children's Bureau its appreciation for their continuing support;

*Resolved*, that the Academy of Pediatrics express its gratitude for the contributions received from the National Foundation for Infantile Paralysis and request the National Office to extend this expression of appreciation to the County Chapters whose support has been essential for the development of State Programs;

*Resolved*, that the Academy express its gratitude for the contributions received from the following commercial firms who have made generous financial contributions to the Central Office of the Academy Study:

Mead Johnson Company  
Pet Milk Company  
Carnation Company

Borden Company  
Lederle Laboratories  
Mennen Company

M and R Dietetic Laboratories

*Resolved*, that the foregoing resolutions be incorporated in the minutes of the Executive Board of the Academy of Pediatrics held at the William Penn Hotel, Pittsburgh, Pa., Feb. 23, 1947, and that a copy of these resolutions be sent to all those named herein.

Respectfully submitted,  
EXECUTIVE BOARD

It was moved by Dr. Stringfield, seconded, and carried that these resolutions be adopted.

The approaching Pan-American Congress was discussed by Drs. Grulee and Hurtado and, by invitation, Drs. Ong and Nicholson of Washington, D. C. The program was presented, the plans for entertainment discussed, and an approximate budget for the expenses of the Congress outlined. A letter was read from Dr. Henry J. Klaunberg, President, Washington Institute of Medicine, regarding publishing the proceedings of the Congress in the Quarterly Review of Pediatrics. It was agreed that this be done and Dr. Grulee said he would like the same thing to appear in the JOURNAL OF PEDIATRICS. After a discussion of the cost of the Congress, and the approximate budget, it was moved by Dr. Spickard, seconded, and carried that the Treasurer make up the deficit from the Academy funds, with the understanding that if there is an assessment for the International Congress, 25 per cent of it will go toward making up the deficit on the Pan-American Congress.

The Secretary read a letter from Carlos Ferrusino of the Sociedad Boliviana de Pediatría.

At the evening session there were present, by invitation, Drs. John A. Anderson of Salt Lake City, and Hugh L. Moore of Dallas, Texas, the editors of the JOURNAL OF PEDIATRICS, and Drs. Hansen, Butler, Faber, Powers, McIntosh, McQuarrie, and Stokes of the editorial board.

Dr. Anderson discussed the facilities for holding a meeting in Salt Lake City. It was the consensus of opinion that a Region IV meeting or a sectional meeting be held in Salt Lake City on September 8, 9, and 10, 1947.

Dr. Moore presented an invitation from Dallas to hold the 1947 annual meeting there. It was moved, seconded and carried that the annual meeting be held on December 8, 9, 10, and 11 in Dallas, Texas.

The question of whether members granted leaves of absence should be catalogued with regular members, received all correspondence, or should be put in a separate category was discussed. It was decided that they should be listed separately with their last known address.

It was moved by Dr. Beaven, seconded and, carried that the initiation fee be increased to \$50.000 on applications received on or after July 1, 1947.

The Secretary read a letter from Dr. Herbert Coe concerning the establishment of a Surgical Fellowship, or Affiliate Fellowship or Surgical Affiliate to cover the admission of men devoted to the study of the surgical problems of infancy and childhood. In the discussion it was stated that in other specialties, such as Allergy and Dermatology, there are men devoting their entire time to diseases of children in these branches. It was moved by Dr. Beaven, seconded, and carried, that a committee be appointed to look into this matter and report at the next meeting. The Chair appointed Drs. Beaven and Munns as the Committee.

There being no further business, the meeting adjourned at 9:50 P.M.

PITTSBURGH, PA., FEB. 26, 1947

### *Abstract of Proceedings*

A meeting of the Executive Board of the American Academy of Pediatrics was held in the Hotel William Penn, Pittsburgh, Pa., Wednesday, Feb. 26, 1947, following the annual business meeting. There were present Drs. Hill, Pease, Bruce, Munns, Spickard, Beaven, Stringfield, Hurtado, Martner, Kennedy, Toomey, Barba, McElhenney, Hubbard, and Grulee. The meeting was called to order by the President, Dr. Lee Forrest Hill.

The first order of business was the consideration of the proposed changes in the by-laws to be acted upon next July. These changes, which will be necessary to instrument the changes incident to the adoption of the plan for redistricting, were discussed and will be submitted to the membership for vote before final action of the Executive Board in July.

It was recommended that the funds remaining in the former Regions be turned over to the Secretary's office with the provision that they be used for any emergency arising, upon recommendation of the Executive Board.

The Rheumatic Fever Committee recommended that the Academy mail a pamphlet on rheumatic fever to each member. This recommendation was approved.

The corrected recommendation of the Committee on the Study of Child Health Services were approved. A Committee consisting of Drs. Stringfield, Hubbard, Sisson, and Grulee was suggested to study the question of publicity, both for the Study and the Academy, and report at the July meeting of the Executive Board of the Academy.

A committee consisting of Dr. Herbert E. Coe as Chairman and Dr. Beaven, was appointed to investigate and report back to the Executive Board at its meeting in July the possibility of enlarging the scope of the membership to include men in allied branches of medicine who were confining their work to children.

A letter from Dr. Henry Poncher regarding the papers on the Rh factor was discussed, and it was decided to ask Dr. Poncher to contact Dr. Diamond about the preparation of a monograph to be distributed to the members of the Academy, the Academy to be responsible for distribution but not for financing publication.

On motion duly made and seconded the meeting adjourned at 6:55 P.M.



# FIFTEENTH ANNUAL MEETING OF THE AMERICAN ACADEMY OF PEDIATRICS

PITTSBURGH, PA., FEB. 24, 25, 26, AND 27, 1947

## ANNUAL BUSINESS SESSION

The annual business session of the American Academy of Pediatrics was held in the Hotel William Penn, Pittsburgh, Pa., on Wednesday, February 26, 1947. The meeting was called to order at 2 P.M. by the President, Dr. Jay I. Durand.

The first order of business was the presentation of the 1947 Awards by Dr. Joseph Stokes, Jr.

**DR. STOKES.**—The Mead Johnson Award is presented yearly at the national meeting of the American Academy of Pediatrics to that pediatrician of 35 years or under who, in the opinion of the Committee on Awards of the Academy, has carried out the most distinguished investigations in his chosen field.

The membership of the Academy will remember that at the last annual meeting in Detroit no Mead Johnson Award was presented. The inability of the Committee to select a suitable recipient for that occasion lay primarily in the enlistment of a major portion of young investigators in the armed services. For this and many other obvious reasons it has appeared appropriate to the Committee that any distinguished work emanating from such younger men in the armed services deserved recognition over and above that work of young investigators who did not have the opportunity of serving in a similar capacity. Also the Committee felt that if work of sufficient value had been conducted over the war period in the armed services by more than one individual, and if the Mead Johnson Company concurred, an award should be made retroactively for the year 1945, as well as for the year 1946. Such work of sufficient value was found, and such concurrence by the Mead Johnson Company was obtained.

The award for 1945 will be presented by a member of the Committee on Awards and the recipient's former teacher, Dr. Grover F. Powers.

**DR. POWERS.**—The recipient of this Award made a distinguished contribution to the war efforts and to preventive medicine in the control of malaria in the South Pacific area from July, 1942, to December, 1944; he later served as acting chief of Preventive Medicine at the beginning of the Okinawa campaign and at headquarters of the Pacific Armed Forces. His comprehensive, confidential report to the Surgeon General served as an inspiration and model for other workers in the field.

The commanding officer, General Earl Maxwell, states that the recipient "began his work on Malaria, as Epidemic Disease Control Officer, at a time when combat conditions in Guadalcanal on the New Hebrides Islands had taken a terrific toll of military personnel. Although there was considerable actual combat, there were eight malaria cases for each combat admission to the hospital. He quickly and efficiently planned and carried out control measures, and effectively lowered malaria and other epidemic disease conditions to a degree where there were practically no new cases contracted in our troops. Within one year on Guadalcanal, malaria rates were reduced to 1/200 of what they had been when he and his subordinates started his intensive campaign against this disease.

"The recipient's tireless energy, his scientific knowledge, and his dauntless courage in pioneering the scientific investigations of tropical medical subjects in the face of severe climatic and other obstacles were an inspiration to all officers and men who served under him. His inquisitive searching and thorough method of attack always created incentive for new knowledge of tropical diseases. His observations and lessons learned were submitted to higher headquarters without delay and were very helpful in planning for further combat missions on the Pacific Islands."

The recipient was for some time resident in pediatrics in the New Haven Hospital and instructor in pediatrics in the Yale University School of Medicine, where he was trained

in clinical epidemiology under the late Dr. James D. Trask. He was a successful practitioner of pediatrics prior to entering on active duty with the Army of the United States as a major with the 39th General Hospital (Yale Unit) and reverted to inactive status four years later with the rank of Colonel. The recipient earned four campaign stars and the bronze star medal to which was added the Oak Leaf Cluster one year after the first citation. His career in the Armed Forces furnishes another inspiring example of the role pediatricians play in military medicine and in the broad field of public health.

The Committee on Awards of the American Academy of Pediatrics in behalf of the Academy takes great pleasure in presenting the Mead Johnson Award of 1945 to Paul Alwain Harper.

DR. HARPER.—Mr. President, Mr. Chairman, and Fellows of the Academy: I wish to express my deep appreciation to the American Academy of Pediatrics for the bestowal of its Mead Johnson Award. In a large sense the honor means that work of this kind does not belong to any individual but is the result of combined efforts of many individuals who are too numerous to mention. The paper which I wish to present at this time will show the attempts by all these groups to solve these problems.

*(Reads paper.)*

DR. STOKES.—The recipient of the Mead Johnson Award for 1946, even during his undergraduate years in the School of Medicine, University of Pennsylvania, showed a distinct aptitude for and a growing interest in the field of medical research. Studies on vitamin D begun during his first and second years were of such significance that he became the recipient at this early period of a first prize award from the School of Medicine for investigations conducted by undergraduates.

During his later clinical hospital training, both at the University of Pennsylvania and under Dr. Edward A. Park at Johns Hopkins Medical School, there was never a time in which he was not conducting able investigations bridging the gap between the laboratory and the patient.

His interest and aptitude for research were strengthened and deepened by two years spent at the Rockefeller Institute for Medical Research with Dr. Leslie Webster, at which time he initiated the use of ultraviolet light for inactivation of rabies virus, a method now used widely in rabies vaccines.

Following his return to Johns Hopkins Medical School he soon was appointed Medical Director of the Sydenham Hospital, where his continued investigations of infectious diseases are familiar to all of us.

When World War II started, he soon became a member of the Commission on Measles and Mumps, Army Epidemiological Board, and later, as a result of a greater opportunity to work with the armed services in the field, he joined the Naval Medical Research Unit No. II, which conducted outstanding investigations centering around Guam during the latter part of the war.

During this war period, in addition to the quality of the work which he will outline to some extent this afternoon, he has indicated his desire and ability to assist wherever his demonstrated talent would count the most.

The Committee on Awards of the American Academy of Pediatrics therefore on behalf of the Academy takes great pleasure in presenting to Dr. Horace L. Hodes, Associate Professor of Pediatrics, Johns Hopkins Medical School, and Medical Director, Sydenham Hospital the Mead Johnson Award for 1946.

DR. HODES.—Mr. President, and Members of the Academy: I should like to express my appreciation to the Academy for the Mead Johnson Award for 1946.

*(Reads paper.)*

DR. STOKES.—In contrast to the Mead Johnson Award, given chiefly for stimulation of younger men or women for research work, The Borden Award permits the Committee a greater latitude of choice. It has no age limit. It is awarded for distinguished work in the field of nutrition.

The citation of this Award will be presented by a grateful and admiring pupil of the recipient, Dr. Allan M. Butler, Professor of Pediatrics, Harvard University Medical School.

DR. BUTLER.—This Borden Award of 1946 is made for experimental studies consistently pursued over the past thirty years on the anatomy of the body fluids and maintenance of concentrations such as sustain the nutrition and function of tissue cells under the vicissitudes of disease.

Studies characterized by a perception, definitiveness, and such scientific significance as to have given the unusual honor to a pediatrician of membership in the National Academy of Science.

Studies conducted by an individual whose breadth of understanding is reflected in the quality of this humor; whose stimulation to and esteem by younger pediatricians are indicated by his being the first president of their Society of Pediatric Research; whose clarity of thought and artistry of exposition has resulted in his lecture syllabus becoming a standard text of undergraduate students, physiologists, and physicians; whose example in clinical investigation, in editing a medical journal and in teaching, has set standards for American Medicine of which his fellow pediatricians are justly proud.

The Committee on Awards of the American Academy of Pediatrics, on behalf of the Academy takes great pleasure in presenting to Dr. James L. Gamble, Professor of Pediatrics and Chairman of the Department of Pediatrics of Harvard University Medical School, the Borden Award of 1946.

DR. GAMBLE.—I am quite unable to find words which will adequately express my appreciation of this large honor from the Academy and to find something suitable to say to the Borden Company is equally difficult. I am astonished to think that the Borden Company would give this award to a pediatrician who believes, for instance, in water and electrolytes. That they are willing to make the Award to such an individual seems to me to indicate the most extraordinary graciousness.

As regards Dr. Butler's kind words, I am sure you will understand that a person has reached the highest pinnacle of gratification when Dr. Butler's words are kind. I say this because Dr. Butler has long been my helpful and my severe critic.

The talk that I was asked to prepare for this meeting is entitled, "Deficits in Diarrhea."\*

THE SECRETARY.—The following men and women have been accepted for active membership:

#### *Region I*

Herman Anfanger, New York, N. Y.  
 Samuel B. Hurwich, Toronto, Ont.  
 Theodore Hunt Ingalls, Southboro, Mass.  
 Harvey Leinbach, Reading, Pa.  
 William C. McCarthy, Pittsburgh, Pa.  
 Rafael R. Muniz, New York, N. Y.  
 Robert D. Nix, Sewickley, Pa.  
 Donald Ross Reed, Tarrytown, N. Y.  
 Lewis J. Schloss, North Plainfield, N. J.  
 Austin H. Schoen, Brooklyn, N. Y.  
 Harry M. Sternberg, Brooklyn, N. Y.  
 Dwain Newton Walcher, New Haven, Conn.  
 David L. Weinstein, Washington, D. C.

#### *Region II*

Fred S. Brooksaler, Dallas, Texas  
 Alphonse Louis Girardin, Jr., Fort Myers, Fla.  
 Angus M. McBryde, Durham, N. C.  
 William Lucas Venning, Charlotte, N. C.

\*Published on page 458 of the May, 1947, issue of the JOURNAL.

*Region III*

Lawrence Breslow, Chicago, Ill.  
 James P. Conway, Shorewood, Wis.  
 Sol Paul Ditkowsky, Chicago, Ill.  
 James William DuShane, Rochester, Minn.  
 A. R. Eveloff, Lake Springfield, Ill.  
 Max Miles Ginsburg, Denver, Colo.  
 Bernard Gumbiner, Chicago, Ill.  
 Harry C. Metzger, Detroit, Mich.  
 Helen Seibert Reardon, Ann Arbor, Mich.  
 Justus B. Roberts, Ottumwa, Iowa  
 Arthur H. Rosenblum, Chicago, Ill.  
 Herschel Sachs, Cincinnati, Ohio

*Region IV*

Talcott Bates, Monterey, Calif.  
 Norman Ward Clein, Seattle, Wash.  
 Alexander Hatoff, Oakland, Calif.  
 William W. Ornduff, Berkeley, Calif.  
 Lawrence E. Reck, San Diego, Calif.  
 James T. Stanton, Bakersfield, Calif.  
 Chieh Sung, San Francisco, Calif.  
 John Charles Wilcox, Claremont, Calif.

*Region V*

Milton Carlow Braga Netto, Rio de Janeiro, Brazil  
 Amador Guerra y Sanchez, Habana, Cuba  
 Rafael de la Portilla, Lavastida, Habana, Cuba  
 Enrique Galan Conesa, Habana, Cuba  
 Lorenzo Exposito Martinez, Habana, Cuba  
 Antonio Carbonell Salazar, Habana, Cuba  
 Alfredo Ceballos Carrion, Guayaquil, Ecuador  
 Pedro J. Alvarez, Caracas, Venezuela  
 Lya Imber de Coronil, Caracas, Venezuela  
 Guillermo Tovar, Caracas, Venezuela

The following requests for Emeritus membership were accepted by the Executive Committee:

Clara E. Hayes, Washington, D.C.  
 Charles Kimball Johnson, Burlington, Vt.  
 Martin D. Ott, Davenport, Iowa  
 Robert A. Strong, Pass Christian, Miss.

The resignation of Dr. John E. Gordon, Boston, Mass., was accepted and Dr. R. R. Struthers, New York City, was granted a year's leave of absence.

It is the unfortunate duty of the Secretary to report to you the deaths that occurred since the last report.

James L. Foster, Pittsburgh, Pa.  
 Justin A. Garvin, Shaker Heights, Ohio  
 Ralph E. Pray, Salinas, Calif.  
 Jose Robalinho de Oliveira, Pernambuco, Brazil  
 William Ewing Sinclair, Orlando, Fla.  
 Charles E. Turcot, Quebec, Que.  
 Henry P. Ledford, Wichita Falls, Texas

The Vice-President, Dr. Lee Forrest Hill, then took the Chair and the President presented his report.\*

\*Published on page 485 of the May, 1947, issue of the JOURNAL.

THE PRESIDENT.—The next item of business will be the reports of Committees. Dr. Joseph Wall will report on pending legislation for the Committee on Legislation.

### Report of the Committee on Legislation

The Hill-Burton Bill, formerly S.191, passed the Seventy-Ninth Congress and is now known as the Hospital Survey and Construction Act of 1946.

Appropriations were made available for State surveys and authorized, but not appropriated, for construction of hospitals and health centers. It is to be hoped that members of the Academy will interest themselves in proposed health facilities for children through advice to and consultation with the various State agencies entrusted with the implementation of this Act. Their aid in selection of localities for child health facilities and in the planning of such should be welcomed by the communities concerned, more especially as in the near future the results of the Survey by the Academy's Child Health Services Study Committee should be at least partly available, as the Director assures us, which would aid in delineating health needs of children in the various states.

S.545, known by the patronymic of the Taft health bill, was introduced in the Senate on February 10, 1947, by Senator Taft (for himself, Mr. Smith of New Jersey, Mr. Ball of Minnesota, and Mr. Donnell of Missouri) and referred to the Committee on Labor and Public Welfare, the new designation of the Committee on Education and Labor, under the reorganization act.

Physicians in general, as well as pediatricians, should be interested in the provisions of this bill, which establishes a National Health Agency by congressional enactment and not by presidential order.

All activities of the Federal government, excepting those of the armed forces and the Veterans' Administration, are to be centralized under this bill. The Health Agency is to be headed by a physician. (Dr. Wall explained the salient features orally.)

S.140, introduced by Senators Fulbright and Taft, proposes the establishment of a new department in the Federal Government of "Health, Education and Security," providing a secretary who shall have cabinet rank.

Under this bill, hearings having been posted for February 28, by the Committee on Expenditures in the Executive Departments, there would be placed a lay intermediary between the health division and the President. Matters of health would be in charge of an Under-Secretary of Health, a physician, of co-equal rank with the Under-Secretary of Education and the Under-Secretary of Security, the latter word replacing the word "Welfare" which appeared in former bills. The Fulbright-Taft bill is largely sponsored by educators and social uplifters who would, no doubt, dominate the Federal structure to be created by the proposed act.

H.R.1980, introduced in the House a few days ago by Representative Howell of Illinois, formulated and sponsored by Mr. George J. Hecht, owner and publisher of *Parents' Magazine*, proposes expansion of funds for school health purposes to be administered by the Children's Bureau. For the first year 12 million dollars is the appropriation named.

As originally planned, this bill proposed enlargement of funds of Title V of the Social Security Act, as amended, by adding to part 4 of Title V the measures in behalf of school health services as proposed by Mr. Hecht and his associates.

In the early construction stages of this bill, the purposes of providing additional funds to be expended under existing statutes, where need could be shown, seemed to be in line with the policies expressed by the Academy at its Detroit meeting, but after numerous consultations by the sponsor with Federal officials, educational authorities, labor representatives and many others, the proposed bill emerges quite unlike the original draft. In fact, the bill as introduced represents the seventh draft modified by various interests.

The participation of educators in school health matters would seem to place unusual power in the hands of those who are neither qualified nor entitled to exercise any degree of dominance in matters affecting the health of children.

The Hecht bill as introduced proposes that the National School Health Services Act be made a separate entity and it is not now proposed as an amendment to existing statutes as incorporated in the Social Security Act.

Because of its actual introduction only a few days ago, the Committee on Legislation has not had time nor opportunity to report favorably or unfavorably on this measure, but will give to it early consideration, with the assistance of Dr. Harold Mitchell, chairman of the Committee on School Health.

Respectfully submitted,

JOSEPH S. WALL, Chairman  
FRANK VAN SCHOICK  
HARVEY F. GARRISON  
W. L. CRAWFORD

THE PRESIDENT.—We have a small surprise for Dr. Wall. All of us appreciate the amount of time Dr. Wall has given to this Legislative Committee and the skill with which he handled it. As an expression of our appreciation the Executive Board has had an illuminated scroll made to present to Dr. Wall. This is the first time that such an honor has ever been given by the Academy. I should like now in recognition of his services, far beyond the call of duty on Dr. Wall's part, to present this citation on the part of the Academy.

DR. WALL.—Mr. President and Members of the Academy: This comes to me as a complete and absolute surprise, for I did not know I was included among the Oscars that have been distributed this afternoon. I deeply appreciate this action on the part of the Committee. I feel it is not due to me, for I did only what every member of the Committee would do if given the job. I am greatly appreciative of this honor.

THE PRESIDENT.—The next item will be the vote on redistricting.

DR. MARTMER.—I will throw on the screen two slides: one a map, showing the states to be included in the redistricting, and the second, giving the number of states in each district with the number of members of the Academy in each district.

While there is a considerable amount of territory in the extreme West and in Region VII, the number of pediatricians in each area who are members of the Academy at the present moment is appreciably equal, and that is the plan, based on an equal representation on a numerical basis.

THE SECRETARY.—I have requested this plan in order to have a fair representation. As it is now, the man on the West Coast has the same amount to say in the Academy of Pediatrics' Executive Board as any five men on the East Coast, and as any three or four men in the Middle West and any two men in the South. This new distribution does not separate the old groups from the standpoint of meetings. Meetings will be held as they have been in the past, but the responsibility for those meetings would be distributed according to the number of members.

DR. H. LESLIE MOORE.—I move that the report be adopted. (Motion seconded.)

THE PRESIDENT.—I would like to hear some discussion. At the meeting of the State Chairmen the other night there was a great deal of difference of opinion; in fact, the preponderance of opinion was that it would be a good thing to let things go as they are.

DR. CRAWFORD BOST, San Francisco.—It appeared to many of the State Chairmen the other night that perhaps this was a hasty movement. There is a movement westward and it seems we should give consideration to geographic lines. In addition to the slide, we should see a relief map of the country. Let us make more chairmen, if you want equal representation.

THE PRESIDENT.—I would like to correct what Dr. Bost said. This is not the recommendation of the Executive Board, it is the recommendation of a special committee which was appointed to make the study. We have not polled the Board but I know there is a great division of sentiment.

THE SECRETARY.—There is no greater increase in the Academy of Pediatrics in California than there is in New York. There are not as many members in the western group as there are in New York, and as yet we have not heard anything from them.

DR. PARK WHITE, St. Louis, Mo.—As the one State Chairman who voted in favor of this proposition, I should like to say something. If we can do anything to abolish sectionalism in the Academy, we ought to do so. I am in favor of the proposition.

THE SECRETARY.—I do not want anyone to get the impression that I am sold on this proposition. It would be simpler for me as secretary of the Society to get along as we have gone on for many years, but in fairness to the membership they should have an opportunity to give an answer.

DR. WHITE.—We have enough members present today to avoid the need for circularization. I move for a vote.

DR. M. K. WYLDER, Albuquerque, N. M.—There is a big shift in population all over the country. We, in Region IV, have lived there for so long that we like each other and we do not want our old lines broken up. I believe that right now is not the time to undertake this thing. I would like to move that the thing be laid on the table until next year. (Motion seconded.)

(The vote on the motion to table was taken and the motion was lost.)

THE PRESIDENT.—Are you ready to vote on the original question, to adopt the report of the Committee? All in favor of the proposed motion please rise. (The vote was 110 in favor, 98 against.)

I think under any system of redistricting the Academy will live. This makes necessary a meeting of the Executive Board this afternoon to set up the new order.

We will ask for a report from the Editorial Board of the JOURNAL.

DR. BORDEN VEEDER.—Some sixteen years ago when the Academy was organized, one of the things that it needed was an official organ. A Committee was organized to see if such a journal could be found. An arrangement finally was made with The C. V. Mosby Company, whereby the Company would undertake the publication of the JOURNAL OF PEDIATRICS, standing all of the losses and receiving any profits. The Academy was to have full charge of the editorial direction of the JOURNAL. None of us had an idea that the JOURNAL would some day become a profitable venture. For a few years, The C. V. Mosby Company lost financially, but in recent years it is obvious that the Company has made a profit. The title of ownership has been always with the Company.

A year ago, a discussion came up in the Editorial Board as to whether or not some financial return from the JOURNAL should go to the Academy. The matter was discussed with The C. V. Mosby Company, and a special committee was appointed to go into the question of ownership of our own journal. The C. V. Mosby Company has made a proposition which would give to the Academy a certain amount of money each year, depending upon the number of advertising pages carried in the JOURNAL. The Company would still own the JOURNAL. The Editorial Board came to the conclusion after long and detailed study and much thought, that the time has come when the Academy should own its own journal. There are two or three methods by which the Academy can own its own journal. One is that it can go into the publishing business, which by all odds is most profitable. Some journals, like the *Annals of Internal Medicine* are owned and operated by their sponsoring societies. Other societies own their own journals but do not look after the business arrangements and arrange with a publisher to conduct the business of the journal on a certain percentage basis or on a certain fee system, while the journal remains the property of the organization. For certain technical reasons the Committee came to the conclusion that it was not practical at the present time for the Academy to undertake the management of the journal through its own office. Two firms were contacted by the Committee and terms were outlined by these firms. Finally the Edi-

torial Board came to the conclusion that it was advisable to accept the plan outlined by Charles C. Thomas, Publisher, of Springfield, Ill., and consequently made certain recommendations, which you will find on page 8 of the Report of the Executive Board, to the Board at its meeting.

There are certain things that must be made clear. Our subscriptions to The C. V. Mosby Company for the Academy as a group runs from July 1 to July 1. Consequently, on the first of July under this plan we terminate our contract or agreement with The C. V. Mosby Company and the JOURNAL OF PEDIATRICS will no longer be the official journal of the American Academy of Pediatrics. It will not be possible to start the new journal before January, 1948, so there will be a lapse of six months without a journal as the official organ of the Academy.

We look on this new journal as an investment for the Academy. There is every reason to believe that in future years the Academy will receive a substantial return on its investment. This will not be true at the start. The Academy is responsible for any loss that may occur as well as being entitled to any profit that may be made. It is necessary for the first year or two, maybe longer, maybe less, to increase the subscription rate for members of the Academy to \$10.00 a year. This is due very largely to the increase in costs in printing in the last year. The cost of printing and paper alone has gone up 20 to 25 per cent. We have recommended that a subscription rate be placed on the new journal at the rate of \$10.00 per member. This year it will be only five dollars because the journal will not start until the first of January. Should there be a profit from the journal in future years, that profit will first be used to reduce the subscription rate to members of the Academy.

After thoroughly going over the matter, this was the recommendation of the Editorial Board to the Executive Board, and the Executive Board agreed to these recommendations. The present Board of the JOURNAL OF PEDIATRICS appointed by the Executive Board of the Academy resigned as of July 1, when the JOURNAL OF PEDIATRICS will no longer be the official journal of the Academy. This same Editorial Board was requested by the Executive Board to undertake the development of the new journal.

**THE PRESIDENT.**—We have been asked by the officers of the International Congress that time be given for a report. Dr. Helmholtz will present it.

**DR. HELMHOLTZ.**—I think you will all be interested to know a little more about the International Congress which will be held in New York, July 14-17, 1947. The second International Congress on Pediatrics was held in Stockholm in 1930, the third in London, the fourth at Rome. At the fourth Congress an invitation was extended to hold the next one in America. The invitation was accepted and plans were made to hold it in Boston in 1940. The development of World War II forced cancellation of the plans. In 1938 at the meeting of the Academy held in Del Monte, the Academy voted to assess its membership \$10.00. With the onset of World War II, the Executive Board of the Academy voted to return the \$10.00 as a credit on yearly dues. After World War II was over, the executive group of the International Congress, depleted by the death of Dr. Blackfan, communicated with a large number of American pediatricians who voted in favor of holding the International Congress in New York, and Dr. L. E. Holt, Jr. was named as Executive Secretary. The difficult question to answer was whether it should be held early or later. Against holding the Congress at an early date was the political restrictions of travel and the financial difficulties, the hopelessness of the financial basis in Europe and the inability of the Europeans to take part in the program. In order that we might have some idea of how the people in Europe felt about it, we wrote to forty European pediatricians and with one or two exceptions they were all in favor of holding the Congress at a very early date. We were interested in knowing other opinions that led us to contact Dr. Alan Gregg of the Rockefeller Institute who had just returned from a trip to Europe and Asia. In talking with him he was very decided that the Congress be held immediately. The fact that the Rockefeller Foundation is making a substantial donation to bring the men over showed that Dr. Alan Gregg was willing to back up his opinion.



He felt that the medical schools in Europe had from three to five times as many students registered as ever before, and only if the pediatricians came over this year would it be possible for them to get away from their work. He also felt that we could give these pediatricians an opportunity to see the development of pediatrics in recent years in this country.

The question of the contribution that the Europeans might make was also discussed. A great deal of work has gone on in England, Switzerland, and Sweden. Experimentally, a great deal of work has been going on in the occupied countries, which started in the Underground and has spread into many places. Dr. Gorter was able to continue his work in Holland in spite of the fact that he was confined to a wheel chair. It seemed to us, in view of the work that was going on, that we could get up an excellent program and that we should hold the Congress. We had decided on September, 1947. We were already going ahead to hold it then when we got information from the hotels in New York that the United Nations were requesting 5,000 extra rooms for September, 1947, so that we could not hold the Congress at this time. So it was decided to hold it in New York in July. While not ideal, that was the time we could be assigned sufficient rooms to take care of the Congress.

From the program that Dr. McIntosh has worked out I feel sure that we will have a very interesting meeting that will be participated in by pediatricians of all the various countries. The American contribution to the program will be largely in the scientific exhibits. Dr. Mitchell of Memphis and Dr. Schwentker of Baltimore, cochairmen of the exhibit committee, have prepared a complete survey of the progress made in the last ten years in American medicine. We expect to have about 175 exhibits, all carefully catalogued so as to make them available in the foreign language. They are trying to have tours for the visitors to the seacoast and as far west as Chicago and St. Louis. We feel we will be able to give these visitors an excellent view of American pediatrics.

The American Pediatric Society, the Section on Pediatrics of the American Medical Association, and the Society for Pediatric Research have all made contributions to the financial support of the Congress, according to their resolutions. I think at this time the Academy should determine what it will do with regard to the Congress.

**THE PRESIDENT.**—Since they are associated to some extent, I will ask for a report on the proposed meeting of Region V for delegates from Central and South America, to be held in Washington just prior to the International Congress. Dr. Grulee, will you tell us something about it?

**THE SECRETARY.**—We will hold the Pan-American Congress in Washington July 9-12, ending on Saturday, the 12th, at the Mayflower Hotel. We are now writing to the men in Latin America of this meeting. I have a list of some 4,500. We have to reach all we can. We do not expect more than 250 to 300 to attend. We are planning some entertainment for them. We will not attempt to have and scientific exhibits. Dr. Hurtado has prepared a program which will be purely and simply a Latin American, United States, and Canadian program. There will, of course, be nothing from Europe. The cost of that meeting will approach \$10,000.00. It has not been entirely covered yet. We have hopes.

**DR. STRINGFIELD.**—In October of last year I had a meeting of our state chairmen in Washington, at which time we discussed the Fifth International Clinical Congress. At that time it was the unanimous opinion of the State Chairmen that the holding of an International Congress at this time was premature. They were also of the unanimous opinion that if and when an International Congress was held, the pediatricians of this country should get behind it to the best of their ability and that we should assess each member \$10.00 in order to assist in financing this venture. Therefore, Mr. President, I would like to move that the pediatricians of this country make every effort possible to assist in making the Fifth International Congress a success, and that the members of the Academy assess themselves \$10.00 to help defray the expenses associated with this undertaking. (Motion seconded and carried.)

**THE PRESIDENT.**—There are several resolutions which have been presented. I will ask the Secretary to read them.

THE SECRETARY.—The first is presented by the State Chairmen:

"*Resolved*, that the State Chairmen of the Academy of Pediatrics recommend that the attention of the appropriate officials be called to the necessity of raising the salaries of Public Health personnel at local, state, and federal levels in order to obtain qualified physicians for these positions."

I move its adoption. (Motion seconded and carried.)

The second resolution reads as follows:

"Your Committee on Mother's Milk Bureaus requests the Academy at this meeting to give its official endorsement and support to a national movement to encourage breast feeding of infants."

JULIUS H. HESS, Chairman

CARL H. LAWS

MINER C. HILL

CLEMENT A. SMITH

WILLIAM J. ORR

I move its adoption. (Motion seconded and carried.)

The following resolutions relate to this meeting in Pittsburgh.

"*Be it resolved*, that the American Academy of Pediatrics express its sincere appreciation to the local members in the Pittsburgh area and to Drs. W. W. Briant, Jr., E. R. McCluskey, and H. T. Price for the splendid cooperation in the planning and conduct of the annual meeting held at the Hotel William Penn Feb. 24 to 27, 1947."

I have never received such cooperation as I received in Pittsburgh. I move its adoption. (Motion seconded and carried unanimously by a rising vote.)

"*Be it resolved*, that the American Academy of Pediatrics express its sincere appreciation of the superior manner in which the Pittsburgh Convention Bureau handled the hotel registrations for the annual meeting of the Academy held Feb. 24 to 27, 1947."

I move its adoption. (Motion seconded and carried unanimously.)

"*Be it resolved*, that the American Academy of Pediatrics express its sincere appreciation to the management of the Hotel William Penn for the splendid cooperation of all the Hotel Executives, as well as the employees, and especially to Mr. William F. Kirk, Sales Manager, Mr. J. D. Stroup, Assistant Sales Manager, and Mr. Louis Berti, during the preparation for and the period of the annual meeting of the Academy held Feb. 24 to 27, 1947."

I want to say my experience with these gentlemen has been entirely satisfactory. I move the adoption of the resolution. (Motion seconded and carried unanimously.)

"*Be it resolved*, that the American Academy of Pediatrics sincerely appreciates the courtesy of the Libby, McNeill and Libby Company, The Mennen Company, Mead Johnson and Company, H. J. Heinz Company, the Joseph Horne Company, and the University of Pittsburgh for providing the special events for members and their wives attending this meeting."

I move its adoption. (Motion seconded and carried unanimously by a rising vote.)

THE SECRETARY.—The following is the report of the Nominating Committee:

#### Report of the Nominating Committee

##### Recommendations.—

For Vice President (President-elect):

John A. Toomey, Cleveland, Ohio

If the redistricting is *not* passed by the members:

For Chairman of Region IV:

Vernon W. Spickard, Seattle, Washington

If the redistricting is passed by the members:

For District I, Oliver L. Stringfield, Stamford, Conn. (1 year).

For District II, Paul W. Beaven, Rochester, N. Y. (2 years).

For District III, Philip S. Barba, Philadelphia, Pa. (2 years).

For District IV, Warren W. Qillian, Miami (Coral Gables), Fla. (1 year).

For District V, James W. Bruce, Louisville, Ky. (2 years).

For District VI, George F. Munns, Winnetka, Ill. (3 years).

For District VII, Thomas J. McElhenney, Austin, Tex. (1 year).

For District VIII, Vernon W. Spickard, Seattle, Wash. (2 years).

For District IX, The representative will be determined by a vote of the Latin-American members at the meeting of the Pan-American Congress in Washington, July 10 to 13, 1947 (3 years).

Respectfully submitted,

EDWARD B. SHAW, Chairman

PRESTON A. MCLENDON

HOWARD J. MORRISON

WYMAN C. C. COLE

THE PRESIDENT.—You have heard the report; are there any further nominations? (No nominations were made.) If not, I should like a motion to accept the Committee's report.

DR. VEEDER.—I so move, that the report be accepted and that the Secretary be instructed to cast the affirmative ballot for those who have been proposed by the Nominating Committee. (Motion seconded and carried unanimously.)

The ballot was cast and the President declared the nominees elected.

THE PRESIDENT.—It now becomes my pleasure to install the President for the coming year, Dr. Lee Forrest Hill of Des Moines. I will ask Drs. Love and Henske to escort Dr. Hill to the platform to receive the gavel.

DR. HILL.—I cannot begin to tell you how much I appreciate the honor conferred upon me by making me your President. The individual who would not be flattered by that would have something wrong with him. I am not unaware of the problems that confront the Academy in the years ahead. It is a healthy sign when we have problems. That is what I am interested in. I want to assure you on the part of the Executive Committee and myself that we will settle the problems of the Academy and keep it going the best we can.

I think we should give a standing vote of appreciation to our past President, Dr. Jay I. Durand.

---

There being no further business, on motion duly made and seconded, the meeting adjourned *sine die*, at 4:30 P.M.

# The Academy Study of Child Health Services

## REPORT OF THE COMMITTEE ON THE STUDY OF CHILD HEALTH SERVICES

The Academy Study is now in full flight in its two-phased quest for factual information on all aspects of health services in every state and pediatric education in every medical school and teaching hospital throughout this country. It has passed from its embryonic stage: the red hot baby has passed through a phenomenal period of growth and development, reaching in stature and efficiency almost that of our able Director, Dr. John Hubbard.

The present stage of the Study of Child Health Services is a critical one. It requires the continued, able, and enthusiastic support of every member of the Academy and each State Chairman. Now is the most important and difficult part of the race. Endurance and fitness will be determining factors. Dr. Hubbard and his central executive staff will stand ready to coach you as you reach first base and bring every possible support to enable you to reach home plate. Many of you have put exhausting work into this Academy project. It is not surprising that some of you have grown weary in its accomplishment. But unless you continue your efforts during this last critical phase, the game will not be won.

You will be interested to know that the Study has been organized in all states but one and we expect this one state to follow soon. About a dozen states have completed the collection of information and have sent the questionnaire schedules to the Central Office for statistical analysis. There are many other states that are nearing completion of the Study. It is anticipated that by the beginning of summer the desired information will have been obtained from all states. Indeed, it is essential that the collection of information be completed by July 1, in order that the data may be tabulated and reported by the end of this year or early in 1948, which is the Academy's goal.

During the past year it has become evident to your Committee and its Executive Staff that in addition to an over-all national report, which is what was originally intended, material should be returned to State Chairmen and their Advisory Committees in order to serve as a basis for recommendations and plans to be formulated at the state and local level. With an appreciation of the importance of state reports, a great deal of time and effort has been put into a preliminary draft of the Study in North Carolina, our Pilot State. This preliminary draft has been prepared for a twofold purpose: so that State Chairmen may have a preview of the information which will be available for all states, and so that the committee appointed by the North Carolina Pediatric Society to draw up a final report may select from the formidable array of tabulated material, those items which appear important for local planning.

Most State Chairmen will be familiar with the table forms which are included in this draft, since the tables constitute a revision of the table forms which were discussed in detail last fall at the regional meetings held in Chicago, San Francisco, and Washington. The data for North Carolina have now been entered in these tables. In the final North Carolina report certain of the tables will be omitted entirely; certain others will be transferred from the appendix to the text to permit easier reference to them. In this draft, all the basic tables have been put together in the appendix, in order that State Chairmen may see the amount and type of data which will be tabulated for each state and from which each chairman may select those facts that, for his particular state, seem sufficiently important to include in his published report.

The Executive Staff has not been concerned with recommendations arising from the facts which the Study has revealed in North Carolina. This is a responsibility which belongs to the duly appointed Committee, which, we hope, will reduce the overwhelming mass of factual data to more appropriate dimensions, as well as prepare the recommendations to serve as a basis for a continuing program.

The preparation of this preliminary draft of the North Carolina report is no small accomplishment and emphasizes the effective working relationship which has been established during the course of this Study between the Academy of Pediatrics, the Children's Bureau and the U. S. Public Health Service. This may be said to represent one of the first fruits of the Study, which, in the long run, may well prove to be one of its most significant features, for we have set the stage upon which similar cooperation may continue in implementing the results of this fact-finding study.

The analysis of the factual data in sufficient detail to be of use for local planning in North Carolina and in all other states has greatly increased not only the work of the Central Office but also the cost of the Study. A year ago there was about \$10,000 in the kitty for the conduct of the Study. That was all, except hope. Now, by virtue of the generous support of many of the Academy's loyal friends, the expenses of the Study have been met to the tune of somewhat over \$1,000,000. I wish to take this opportunity to express the gratitude not only of your Committee but the Academy as a whole to those who have helped us so generously.

We have received a grant of \$116,000 from the National Foundation for Infantile Paralysis. The National Institute of Health has given us \$128,550.00, with the promise of more to come for the statistical analysis. We have received a grant from the Field Foundation of New York, and contributions from the Mead Johnson Company, M. & R. Dietetic Laboratories, The Pet Milk Co., Carnation Company, Lederle Laboratories, The Borden and The Mennen Companies. I wish also to congratulate the State Chairmen for the success with which they have financed their own state programs from public and private sources to a total figure of about \$450,000.

In addition to these State studies, which are now nearing completion, the second major phase of the Study has been developed during the past year. I refer to our evaluation of Pediatric Education in all the seventy medical schools of the country and in the teaching hospitals. Dr. John Mitchell of Philadelphia has been appointed as Director of this branch of the Study and is now touring the country spending two or three days in each medical school. A subcommittee has been appointed to develop this part of the Study. Dr. James Wilson is its chairman. It consists of six additional professors of pediatrics, one from each of different areas of the country, so that each member of the Committee may be responsible for the Study in about ten medical schools in his area.

Your Committee has been greatly concerned about the future of the Study. The question is, what are we going to do with the factual data? Through the wisdom of your Executive Board, a follow-up Committee of Nine has already been formed. After our final report is made, this new Committee will make recommendation on a national level—further cooperative efforts with national groups and act as advisers on the state level. The function of the Committee cannot be entirely envisaged, but it is fair to say that the improvement of child health in this country may rest in its hands. The members of this Committee are Dr. James Wilson, Chairman, Drs. Powers, London, Poncher, Kennedy, Sisson, Thelander, Wheatley, and Webb. This Committee has already met, and it is reasonable to express the hope that the Director of the first Committee will continue in the activities of the Academy through this new group.

Respectfully submitted,  
WARREN R. SISSON, Chairman.

## The Social Aspects of Medicine

The article on the Health Insurance Plan of Greater New York by Dr. Ann Kent and Dr. Dean A. Clark, the Director, was specially prepared for this column. As will become immediately apparent to the reader, the Plan possesses noteworthy features: First, it brings to the subscribers the finest kind of comprehensive medical care, including preventive care. Most of the medical plans in operation in this country furnish only general practitioner care. Second, the Plan furnishes good compensation to the physicians working under it; for example, it allows for \$10,000 salaries to its full-time physicians. The Plan embodies, therefore, two principles which must be at the basis of any sound medical care plan, namely, the supply of all the advantages of preventive medical care and specialist service to its clientele and adequate financial compensation coupled with security to its physicians. I might point out additionally that it possesses the great merit of retaining the general practitioner in the hub position of family doctor.

The Plan has, of course, a great deficiency, in that it does not include the lowest income groups, who still remain without the pale; indeed, it suffers greatly from its sharp limitation to certain industrial groups within the \$5,000 income level. How can such kind of comprehensive medical care be extended so that it will include all who need it? That is the great question. Senator Taft is quoted in *Medical Economics* as saying: "Moreover, the man who is helped by the State must not be quite so well off as the man who earns his own living and stands on his own feet." (*Medical Economics*, vol. 24, p. 81, 1946.) I hope that this reactionary, undemocratic point of view is as repugnant to the readers of the column as to me. In the first place, the best and most comprehensive medical care is more required at the lowest economic levels than at any others. If the lowest income groups could have the very best medical care, some of them would be lifted out of the indigent category, for in many instances they are indigent because of relievable circumstances, chief among which is poor health. Further, the down-and-out groups furnish the fertile soil for communism and the way to eradicate communism is to remove the conditions which breed it. In the second place, the term "medically indigent" is a relative one denoting merely a fractional relationship between the degree and duration of illness in the numerator and ability to pay in the denominator. Most of us would become medically indigent if there were in our families illnesses of sufficient magnitude and duration. Even in a doctor's family the bills for hospital and nursing care can be disabling. If Senator Taft was correctly quoted, his remark implies that the man who must be helped by the State suffers from inferior character. His remark is reminiscent of the refrain:

"Rattle his bones over the stones  
He's only a pauper whom nobody owns."

In the last verse of "The Pauper's Last Ride," the refrain changed to: "He is a pauper whom only God owns."

Before concluding, I might point out another great deficiency in the H.I. Plan, namely, that the required hospital insurance covers only catastrophic illness. The Plan, therefore, does not relieve the subscribers from the very worst illness situations which can occur, i.e., even under the Plan a subscriber may become "medically indigent."

In summary, the criticisms of the Plan can all be reduced to the single criticism of limitation of scope, not incorrectness in design. Perhaps its success will make its enlargement and extension a natural evolution.

E. A. P.

## MATERNAL AND CHILD HEALTH BENEFITS UNDER THE HEALTH INSURANCE PLAN OF GREATER NEW YORK

ANN KENT, M.D., M.P.H.,<sup>\*</sup> AND DEAN A. CLARK, M.D.†  
NEW YORK, N. Y.

Within the past five or six decades there has been a tremendous widening of the field of medical knowledge. Complete medical care can no longer be given by any one physician. A general physician today must work with one or more of the increasing number of specialists in order to provide his patients with care which meets the highest modern standards. The cost and complexity of this kind of care have led to the development of group practice by physicians. This system of practice calls for the close professional cooperation of general physicians and specialists sharing equipment and personnel. Group practice first grew out of the association of doctors in charity clinics and teaching hospitals. Many well-known groups are now in operation, not primarily associated with hospitals, such as groups in private practice, or associated with consumer cooperatives or with industrial concerns. There are many different ways of financing group practice, as, for instance, by endowments and gifts, public funds, subsidies from government or industry, and finally by fee for service or by a plan of periodic prepayments to the group which undertakes to give care.

The Health Insurance Plan of Greater New York combines the private practice of group medicine with a system of financing by means of periodic prepayments by subscribers to the Plan. The HIP is incorporated as a nonprofit membership corporation; it is a voluntary undertaking. Eligibility for enrollment is limited to persons whose income is \$5,000 or less. Enrollment is restricted to employed groups of twenty-five or more, and each employed group must constitute 75 per cent or more of an employment unit: a whole firm or some department or subdivision thereof. The subscriber's spouse and unmarried children under 18 years of age are also eligible for benefits. There are three classes of premium: 56 cents per week for an employee without dependents, \$1.12 per week for an employee with one dependent and \$1.68 per week for an employee with two or more dependents. In each case, the employer is expected to pay at least half of the premium. Every subscriber to HIP is required also to belong to a prepaid hospitalization plan.

The benefits to which an HIP subscriber is entitled include complete medical, surgical, and obstetrical care in the home, office, or group center and in the hospital; laboratory and x-ray procedures; physiotherapy and radiotherapy; visiting nurse service in the home and ambulance service from home to hospital. Insured persons are also entitled to preventive measures such as health education, periodic health examinations and immunizations. Benefits not included are cosmetic surgery, treatment for acute alcoholism and drug addiction, and care for tuberculosis, psychiatric illness and other chronic illnesses which require treatment in institutions other than hospitals for general care. Drugs, appliances, and eye glasses are not supplied. Dental care is not included at the present, but it is hoped that this service may be started for children of subscribers before long.

The medical service is provided by physicians who have organized themselves into groups which have met the medical standards drawn up by the HIP Medical Control Board. Any physician licensed in New York State is eligible to participate in the HIP program, provided that he meets the minimum medical standard and becomes affiliated with a medical group. He is not required to give up his private practice. The standards for individual physicians vary according to whether the man wishes to be a general practitioner or a specialist in his group. The group as a whole must be large enough eventually to provide medical care for a minimum of 10,000 people, allowing for a maximum ratio of one full-time

\*Supervising Physician, Secondary School Health Services, New York City Health Department.

†Medical Director, Health Insurance Plan of Greater New York.

physician or the equivalent in part-time service for each \$800 insured persons. In each group twelve basic specialties must be covered and in addition the group must include five to six general practitioners. The basic specialties are: internal medicine, general surgery, obstetrics and gynecology, pediatrics, otolaryngology, ophthalmology, urology, orthopedics, dermatology, neuropsychiatry, radiology, and pathology.

The individual physicians and the group as a whole are passed upon by the Medical Control Board of the HIP. This Board is made up of physicians appointed by the Board of Directors of HIP and its function is to promulgate and maintain high professional standards in the medical groups. It includes representatives of the five county medical societies of New York City and the New York Academy of Medicine. Before a group is ready to give service it must provide either a medical center to house all or part of its doctors or an administrative headquarters where the business of the group can be transacted, while the individual physicians provide service in their own offices. The contract which the group signs with the HIP contains a clause, however, in which the group undertakes to provide a medical center as soon as it becomes possible to do so. In return for providing the medical service outlined in the foregoing paragraphs, the group receives from HIP \$19.20 per insured individual per year. This allows for an average net income of about \$10,000 for each full-time physician of the group. The HIP pays the capitation to the group as a whole and does not undertake to regulate its distribution among individual members. The income of the group physicians are therefore subject to the groups internal arrangements and may depend upon age, experience, type of practice, amount of time devoted to the group, and other factors.

Subscribers to the HIP have a free choice of which group to join. Prospective enrollees are given booklets in which the names and addresses of the members of the various medical groups are listed. Subscribers are asked to choose from among those groups which have agreed to serve the area in which the subscriber's residence is located. There are now twenty-two medical groups, including some 700 physicians, providing service to the initial HIP subscribers and dependents. In order to assure continuity of service, once a subscriber has chosen a group from which he wishes to obtain service, he is asked to select as his family physician one of the general physicians of the group. This general physician will be the subscriber's family doctor from then on and will call upon the services of the group's specialists and facilities as needed.

The foregoing has been discussion of the HIP in general terms. Specific advantages to maternal and child health should be emphasized. There is no waiting period for coverage for obstetrics, and there is no limit to the duration or type of obstetrical care. Care of the infant is assumed from the time of birth; the first ninety days of life are not excluded as is the case in some other insurance plans. Overloading of physicians is guarded against by limiting the load to a maximum ratio of 800 insured persons per full-time physician or his equivalent in part-time service.

Continuity of medical service is very often lacking when families, particularly in low income groups, attempt to secure medical care without guidance. They frequently shop around from private physician to private physician and from one clinic to another and such preventive medical care as they do receive is practically always given in a free clinic by doctors who have no contact with them when they are ill. This very inefficient type of care is eliminated under the HIP because the family physician will bear the responsibility for the care of the subscriber and his family in sickness and in health.

The family physician is free to make the fullest possible use of his group's specialists without additional charge to his patients. Ready availability of specialists' services is particularly valuable in the field of maternal and child health because of the great frequency with which the need for this kind of consultation arises in general practice. Although, as the HIP groups are now constituted, it may not be possible for the obstetrician, if he is the only one in the group, to give all the prenatal care himself, every group's obstetrician has supervision over and responsibility for all obstetrical services including pre- and postnatal care and is available for the actual delivery. The group's pediatrician is likewise avail-



able for consultation in cases of illness among children of subscribers and, in most of the medical groups all child care will be provided by pediatricians. In any case, it will be the pediatrician's responsibility to see that the physicians of the group give child care according to the best modern standards.

Hospitalization within the limits of the community's resources is assured because each HIP subscriber is required to belong to a hospital plan as a condition of being accepted for HIP medical benefits.

The HIP will conduct a health education program among its subscribers emphasizing preventive medical care and other factors in healthy living for everyone at all ages, and the participating physicians are urged to make provisions for such care in arranging the work of the groups.

It should also be noted that the Plan is not limited to indigents alone. By setting the top income eligible for enrollment at \$5,000, families are included who otherwise probably receive very mediocre medical care; they cannot afford to buy the best available and they will not accept the often excellent care given in free clinics. On the other hand, the rather high premiums required to finance the HIP do not become a deterrent to potential subscribers in the lower income brackets because of the fact that in each case the subscriber's employer shares at least half of the cost. This sum, as previously stated, does not increase beyond the amount required to insure an employee and two dependents, regardless of the actual size of the subscriber's family. There is very great interest in this policy of sharing the cost because most employers have come to realize the long-range wisdom of aiding their employees to secure good health service, because they feel that employees are more loyal and efficient when they are in good health themselves, free from concern over family medical cost, and have a feeling of security regarding health problems in general.

In conclusion, the comprehensive program of the HIP offers great advantages, both in preventive medicine and in therapy, to maternal and child health. The experience that will accumulate when the program is operating on a large scale will be of great value in defining more clearly the health needs of mothers and children and in demonstrating practicable methods of meeting these needs.

## Communication

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Dear Dr. Veeder:

The newly appointed Committee on Hospitals and Dispensaries of the American Academy of Pediatrics has been asked to study construction standards for Nursery Departments, Pediatric, and Contagious Disease units, as set forth in the Hospital Survey and Construction Act (Public Law 725—Seventy-ninth Congress).

To assist the Committee in formulating recommendations to the proper authorities for additions or changes, it seemed appropriate to publish these standards and to request suggestions and criticisms from members of the Academy, pediatricians, and general practitioners interested in developing plans, under the provisions of the Act, for hospital construction in their local communities. It is to be emphasized that these standards are minimum requirements for construction and equipment as required by the Federal Hospital Council and are in no way concerned with regulations for operation or management of pediatric units.

The following standards for Pediatric and Contagious Disease units are copied from Title 42—Public Health, Chapter 1—a reprint from the Federal Register, Division of Hospital Facilities:

### *Nursery Department*

#### Full-term nursery:

Area required: Not less than 24 square feet per bassinet, 30 square feet recommended.

Number of bassinets: No more than 12 bassinets in each full-term nursery, 8 recommended.

Examination and workroom: One examination and workroom between each two full-term nurseries.

#### Premature nursery (to be provided where four or more premature bassinets will be required):

Area required: 40 square feet per bassinet.

Number of bassinets: Not more than six in each premature nursery.

Each premature nursery to have own work areas.

#### Suspect nursery:

Area required: 40 square feet per bassinet.

Number of bassinets: Approximately 20 per cent of full-term bassinets. Not more than 3 bassinets in each suspect nursery.

Workroom: One workroom for each two suspect nurseries.

Formula room: Location in nursery area or near kitchen optional.

### *Contagious Disease Nursing Unit*

#### Patient rooms:

A maximum of two beds in each room separated by a glazed partition.

Patient rooms shall have a view window from corridor.

Each patient room shall have a separate toilet and lavatory in the room.

Each nursing unit shall contain:

Nurses' station

Utility room

Nurses' workroom

Treatment room

Scrub sinks strategically located in the corridor.

Kitchen with separated dishwashing room adjacent

Doctors' locker and gown room  
 Nurses' locker and gown room  
 Janitors' closet  
 Storage closet  
 Stretcher alcove.

### *Pediatric Nursing Unit*

#### General:

Each bed in a multibedroom shall be in a clear glazed cubicle.  
 Each room shall have a lavatory.  
 Patients' rooms wherever possible should have clear glazing between them and in the corridor partitions.

#### Minimum area:

80 square feet per bed in two-bed rooms and over.  
 100 square feet in single rooms.  
 40 square feet per bassinet in nurseries.

#### Each nursing unit shall contain:

Nursery  
 Isolation suite  
 Treatment room  
 Nurses' station with adjoining toilet  
 Utility room  
 Floor pantry  
 Play room or solarium  
 Bath and toilet room: with raised, free-standing tub and 50 per cent children's fixtures  
 Bedpan facilities  
 Wheelchair and stretcher alcove  
 Janitors' closet  
 Storage closet.

It is requested that suggestions for additions and changes, or criticisms of the above standards be forwarded to Dr. John McK. Mitchell, Chairman of the Committee on Hospitals and Dispensaries, Cushman Road and Lancaster Avenue, Rosemont, Pa.

(Signed) Montgomery Blair, Jr., M.D.  
 for the Committee on Hospitals and Dispensaries.

## Academy News and Notes

The following members have been released from military service:

Edward D. Anderson, Minneapolis, Minn. (*Navy*)  
 Donn James Barber, Greeley, Colo. (*Army*)  
 Frank J. Jacobson, Providence, R. I. (*Army*)

### Erratum

In the article by Karp and Teuscher entitled "General Anesthesia in the Difficult Pedodontic Patient" in the March, 1947, issue of the JOURNAL on page 320, the following correction should be made in Table I: for the age group 1 to 2 years under atropine, the dosage should read 0.065 mg.

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